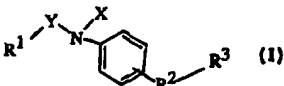
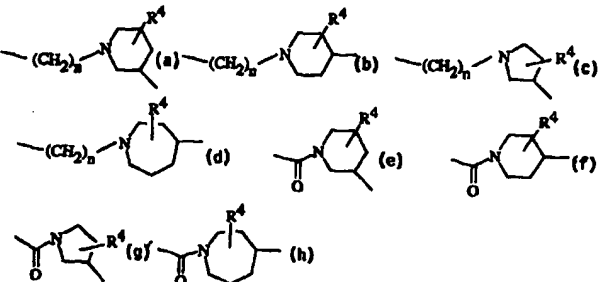




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 211/58, A61K 31/445, C07D 211/56, 211/60, 211/62, 401/06, 405/04, 405/06</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/43658 (43) International Publication Date: 2 September 1999 (02.09.99)</p>
<p>(21) International Application Number: PCT/US98/25007 (22) International Filing Date: 20 November 1998 (20.11.98) (30) Priority Data: 60/076,141 27 February 1998 (27.02.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HU, Lain-Yen [-/US]; 4881 S. Ridgeside Circle, Ann Arbor, MI 48105 (US). RYDER, Todd, Robert [US/US]; 521 N. Ashley Street, Ann Arbor, MI 48103 (US). RAFFERTY, Michael, Francis [US/US]; 3711 Rolling Ridge Court, Ann Arbor, MI 48105 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: HETEROCYCLIC SUBSTITUTED ANILINE CALCIUM CHANNEL BLOCKERS</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  </div> <p>(57) Abstract</p> <p>The present invention provides compounds that block calcium channels having Formula (I): wherein each n is independently 0 to 3; R¹ is C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or arylalkyl; Y is (a), (b), (c), (d), (e), (f), (g) or (h); X is C₁-C₈ alkyl, C₁-C₈ substituted alkyl, C₂-C₈ alkenyl, C₂-C₈ substituted alkenyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl; R² is absent, -O-, (CH₂)_n-, O(CH₂)_n-, (CH₂)_nO-, N(R⁵)(CH₂)_n-, (CH₂)_nN(R⁵)-, S(CH₂)_n-, (CH₂)_nS-, -C≡C-, or -C=C-; R³ is monocyclic aryl, substituted monocyclic aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, substituted C₃-C₁₀ cycloalkyl; R⁴, R⁵ are independently H or C₁-C₈ alkyl. The present invention also provides methods of using the compounds of Formula (I) to treat stroke, cerebral ischemia, head trauma, epilepsy, asthma, amyotrophic lateral sclerosis, or pain and to pharmaceutical compositions that contain the compounds of Formula (I).</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

-1-

HETEROCYCLIC SUBSTITUTED ANILINE CALCIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

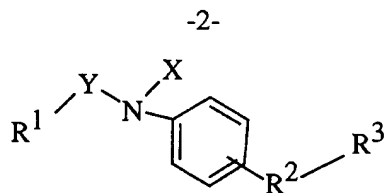
5 The present invention relates to compounds that act to block calcium channels; methods of using the compounds to treat stroke, cerebral ischemia, pain, head trauma, asthma, amyotrophic lateral sclerosis, or epilepsy; and to pharmaceutical compositions that contain the compounds of the present invention.

BACKGROUND OF THE INVENTION

10 The entry of excessive amounts of calcium ions into neurons following an ischemic episode or other neuronal trauma has been well documented. Uncontrolled high concentrations of calcium in neurons initiates a cascade of biochemical events that disrupts normal cellular processes. Among these events are the activation of proteases and lipases, breakdown of neuronal membranes and the formation of free radicals, which may ultimately lead to cell death. Several
15 types of calcium channels have been discovered and called the L, N, P, Q, R, and T types. Each type possesses distinct structural features, functional properties and cellular/subcellular distributions. Type selective calcium channel blockers have been identified. For example, SNX-111 has been shown to be a selective N-type calcium channel blocker and has demonstrated activity in a number of models of
20 ischemia and pain (Bowersox S.S., et al., Drug News and Perspective, 1994:7:261-268 and references cited therein). The compounds of the present invention are calcium channel blockers that can block N-type calcium channels and can be used to treat stroke, pain, cerebral ischemia, head trauma, and epilepsy.

SUMMARY OF THE INVENTION

25 The present invention provides compounds having the Formula I

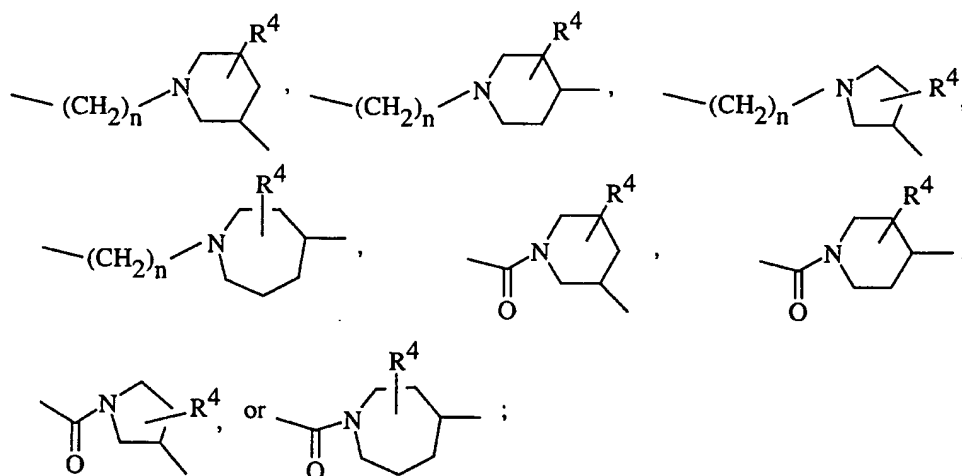


wherein

each n is independently 0 to 3;

R^1 is C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, substituted C_3 - C_8 cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_2 - C_8 alkenyl, C_3 - C_8 cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or arylalkyl;

Y is



X is C_1 - C_8 alkyl, C_1 - C_8 substituted alkyl, C_2 - C_8 alkenyl, substituted C_2 - C_8 alkenyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl;

R^2 is absent, -O-, $(CH_2)_n$ -, $O(CH_2)_n$ -, $(CH_2)_nO$ -, $N(R^5)(CH_2)_n$ -, $(CH_2)_nN(R^5)$ -, $S(CH_2)_n$ -, $(CH_2)_nS$ -, -C=C-, or -C≡C-;

R^3 is monocyclic aryl, substituted monocyclic aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, substituted C_3 - C_{10} cycloalkyl;

-3-

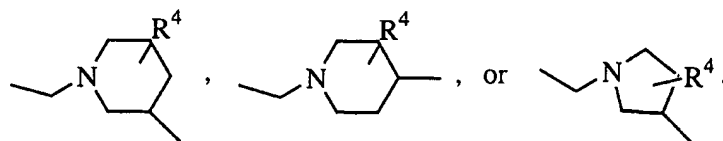
R^4 , R^5 are independently H or C_1 - C_8 alkyl; and

the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In a preferred embodiment of the compound of Formula I, R^2 is $O(CH_2)_n$ - or $-(CH_2)_n$ - and R^3 is phenyl.

5 In another preferred embodiment of the compounds of Formula I, X is C_2 - C_8 alkenyl or C_1 - C_8 alkyl and

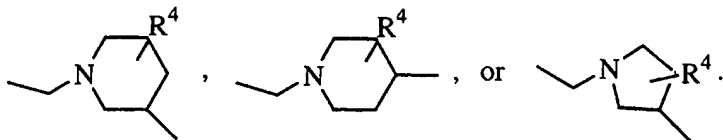
Y is



10 In another preferred embodiment of the compounds of Formula I, R^4 is hydrogen and R^1 is 3,3-dimethylbutyl.

In another preferred embodiment of the compounds of Formula I, R^3 is phenyl;

Y is



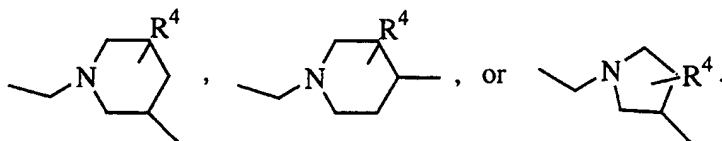
15 R^4 is hydrogen;

X is 3-methyl-but-2 enyl; and

R^1 is C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, substituted C_3 - C_8 cycloalkyl, heterocycloalkyl, substituted heteroalkyl, C_2 - C_8 alkenyl, substituted C_3 - C_8 cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or arylalkyl.

20

In another preferred embodiment of the compounds of Formula I, Y is



In another preferred embodiment of the compounds of Formula I, X is 3-methyl-but-2 enyl or 3-methylbutyl.

In another preferred embodiment of the compounds of Formula I, R¹ is C₁-C₈ alkyl, phenyl, pyrrolyl, piperazinyl, imidazolyl, pyridyl, or pyranlyl.

In another preferred embodiment of the compounds of Formula I, R⁴ is hydrogen.

5 In a most preferred embodiment of the present invention, the compounds are:

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

10 (4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

15 4-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-ylmethyl}-phenol;

(4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

20 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(1H-imidazol-4-ylmethyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pyridin-2-ylmethyl)-piperidin-4-yl]-amine;

25 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-amine;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-2-yl]-methanone;

30 {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-3-yl]-methanone;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-4-yl]-methanone;

- {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-
[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;
- {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-
[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;
- 5 {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-
[6-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;
- {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-
[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;
- {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-
10 [3-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;
- (4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-(3-methyl-
butyl)-amine;
- 4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-(3-
methyl-butyl)-amine;
- 15 (4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-piperidin-4-yl]-(3-methyl-
butyl)-amine;
- (4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-4-yl]-(3-methyl-
butyl)-amine;
- (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-
20 piperidin-4-yl]-amine;
- (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(4-methylsulfanyl-benzyl)-
piperidin-4-yl]-amine;
- (4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-4-yl]-(3-
methyl-butyl)-amine;
- 25 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-4-yl]-(3-
methyl-butyl)-amine;
- (4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-
butyl)-amine;
- (4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-3-yl]-(3-
30 methyl-butyl)-amine;
- (4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-piperidin-3-yl]-(3-methyl-
butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-3-yl]-amine;

5 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-3-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

10 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

15 (4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

20 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-3-yl]-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-3-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

25 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

30 (4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-pyrrolidin-3-yl]-amine;

5 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(4-methylsulfanyl-benzyl)-pyrrolidin-3-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

10 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-4-yl)-(4-benzyloxy-phenyl)-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

15 (4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-3-yl)-(4-benzyloxy-phenyl)-(3-methyl-butyl)-amine;

20 (4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-3-yl)-(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amine;

25 (4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

30 (1-Benzo[1,3]dioxol-5-ylmethyl-pyrrolidin-3-yl)-(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

N-Benzyl-N'-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

5 N-Benzyl-N'-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

N-Benzyl-N'-{[1-(3,3-dimethyl-butyl)]-piperidin-4-yl}-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

10 N-Benzyl-N'-[1-(4-bromo-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

N-Benzyl-N'-[1-(4-methoxy-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-(4-phenethyl-phenyl)-amine;

15 (1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-4-yl)-(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

20 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-4-yl]-amine;

4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

25 4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pentyl-piperidin-4-yl)-amine;

30 4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

-9-

- 4-Benzyloxy-phenyl)-(3-methyl-butyl)-(1-pentyl-piperidin-4-yl)-amine;
4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-methyl-butyl]-piperazin-2-yl]-methanone;
4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;
5 4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;
4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;
10 4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;
4-Benzyloxy-phenyl)-(3-methyl-butyl)-(1-pentyl-piperidin-3-yl)-amine;
{3-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-3-methyl-butyl)-piperazin-2-yl]-methanone;
15 3-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;
3-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;
4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;
20 4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;
4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pentyl-piperidin-3-yl)-amine;
25 3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;
3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;
3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;
30 4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

-10-

4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pentyl-pyrrolidin-3-yl)-amine;

5 3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-pyrrolidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-pyrrolidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

10 3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-pyrrolidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-(3-methyl-but-2-enyl)-amine;

4-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-butan-2-ol;

15 (4-Benzyloxy-phenyl)-(1-furan-2-ylmethyl-piperidin-4-yl)-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-phenyl-propyl)-piperidin-4-yl]-amine;

20 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-phenethyl-piperidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-methanesulfonyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-fluoro-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

25 [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

4-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-butan-2-ol;

30 (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

[1-(4-Fluoro-benzyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-(1-pyridin-3-ylmethyl-piperidin-4-yl)-amine;

[1-(1H-Imidazol-4-ylmethyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

5 2-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-propan-1-ol;

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

10 (4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

[1-(4-Fluoro-benzyl)-piperidin-4-yl]-(4-isopropoxy-phenyl)-(3-methyl-but-2-enyl)-amine;

1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropoxy-phenyl)-(3-methyl-but-2-enyl)amine;

15 [4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

4-(3,3-Dimethyl-butyl)-phenyl]-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

20 [1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-[4-(3,3-dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-amine;

(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

4-{4-[(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-butan-2-ol;

25 (4-Cyclohexylmethoxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

[1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-[4-(4-fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-amine;

30 (S)-1-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-2-hydroxy-4-methyl-pentan-1-one;

(S)-2-Hydroxy-1-{4-[(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-4-methyl-pentan-1-one;

(3-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

5 [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-(4-phenethyl-phenyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

10 (4-Benzyloxyphenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(1-Cyclohexylmethyl-piperidin-4-yl)-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-amine;

15 (1-Cyclohexyl-piperidin-4-yl)-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-[1-(3,3,3-trifluoropropyl)-piperidin-4-yl]-amine;

20 (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(3,3,3-trifluoropropyl)-piperidin-4-yl]-amine;

(1-Furan-3-ylmethyl-piperidin-4-yl)-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-(1-thiophen-3-ylmethyl-piperidin-4-yl)-amine;

25 [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-[4-(furan-3-ylmethoxy)-phenyl]-(3-methyl-butyl)-amine;

[1-(4-Fluoro-benzyl)-piperidin-4-yl]-[4-(furan-3-ylmethoxy)-phenyl]-(3-methyl-butyl)-amine;

30 [4-(Furan-3-ylmethoxy)-phenyl]-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

-13-

[4-(4-Fluoro-benzyloxy)-phenyl]-[1-(4-fluoro-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-phenyl-piperidin-4-yl)-amine;

5 (4-Benzyloxy-phenyl)-[1-(4-fluoro-phenyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(4-trifluoromethyl-phenyl)-piperidin-4-yl]-amine;

10 [4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-(1-pyridin-2-ylmethyl-piperidin-4-yl)-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-(1-pyridin-4-ylmethyl-piperidin-4-yl)-amine;

4-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-ylmethyl}-phenol;

15 (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine;

(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-3-ylmethyl)-piperidin-4-yl]-amine;

20 [4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-[1-(1H-pyrrol-3-ylmethyl)-piperidin-4-yl]-amine;

(trans)-2-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-cyclohexanol;

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-cyclohexylmethyl-amine;

25 (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-ethyl-amine;

Benzyl-(4-benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

30 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-3-ylmethyl)-piperidin-3-yl]-amine;

(1-Benzyl-piperidin-4-yl)-(3-methyl-butyl)-[4-(pyridin-3-ylmethoxy)-phenyl]-amine;

-14-

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine; and

(4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine.

5 Also provided is a pharmaceutical composition comprising a compound of Formula I.

Also provided is a method of blocking calcium channels, the method comprising administering to a patient in need of calcium channel blocking, a therapeutically effective amount of a compound of Formula I to block calcium
10 channels.

In a preferred embodiment of the method, the calcium channels are N-type calcium channels.

In another embodiment, the present invention provides a method of blocking N-type calcium channels, the method comprising administering to a patient in need of N-type calcium channel blocking a therapeutically effective amount of a compound of Formula I effective to block N-type calcium channels.
15

The invention also provides a method of treating stroke, the method comprising administering to a patient having or having had a stroke a therapeutically effective amount of a compound of Formula I.

20 The invention also provides a method of preventing a stroke, the method comprising administering to a patient at risk of having a stroke a therapeutically effective amount of a compound of Formula I.

The invention also provides a method of treating cerebral ischemia, the method comprising administering to a patient having cerebral ischemia a therapeutically effective amount of a compound of Formula I.
25

The invention also provides a method of treating head trauma, the method comprising administering to a patient having head trauma a therapeutically effective amount of a compound of Formula I.

Also provided is a method of treating epilepsy, the method comprising administering to a patient having epilepsy a therapeutically effective amount of a compound of Formula I.
30

-15-

Also provided is a method of treating pain, the method comprising administering to a patient having pain a therapeutically effective amount of a compound Formula I.

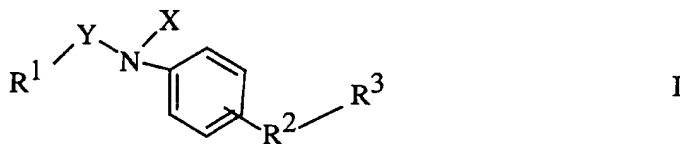
5 Also provided is a method of treating asthma, the method comprising administering to a patient having asthma a therapeutically effective amount of a compound Formula I.

Also provided is a method of treating amyotrophic lateral sclerosis, the method comprising administering to a patient having amyotrophic lateral sclerosis a therapeutically effective amount of a compound Formula I.

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds having the Formula I



wherein

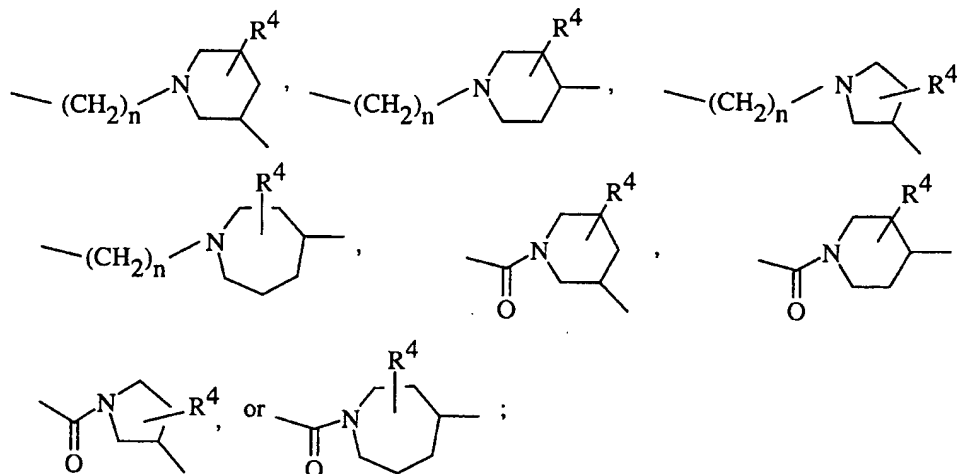
each n is independently 0 to 3;

15

R¹ is C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or arylalkyl;

-16-

Y is



X is C_1 - C_8 alkyl, C_1 - C_8 substituted alkyl, C_2 - C_8 alkenyl, substituted C_2 - C_8 alkenyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl;

R^2 is absent -O-, $(CH_2)_n$ -, $O(CH_2)_n$ -, $(CH_2)_nO$ -, $N(R^5)(CH_2)_n$ -, $(CH_2)_nN(R^5)$ -, $S(CH_2)_n$ -, $(CH_2)_nS$ -, $-C=C-$, or $-C\equiv C-$;

R^3 is monocyclic aryl, substituted monocyclic aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, substituted C_3 - C_{10} cycloalkyl;

R^4 , R^5 are independently H or C_1 - C_8 alkyl; and

the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

The term "alkyl" means a straight or branched chain hydrocarbon.

Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, sec-butyl, pentyl, and hexyl.

The term "alkoxy" means an alkyl group attached to an oxygen atom.

Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy, and isobutoxy.

The term "halogen" includes chlorine, fluorine, bromine, and iodine.

The term "alkenyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon double bond.

-17-

The term "aryl" means an aromatic hydrocarbon. Representative examples of aryl groups include phenyl and naphthyl.

The term "heteroatom" includes oxygen, nitrogen, and sulfur.

5 The term "heteroaryl" means an aryl group wherein one or more carbon atom of the aromatic hydrocarbon has been replaced with a heteroatom. Examples of heteroaryl radicals include, but are not limited to, pyridyl, imidazolyl, pyrrolyl, thienyl, furyl, pyranlyl, pyrimidinyl, pyridazinyl, indolyl, quinolyl, naphthyridinyl, and isoxazolyl.

10 The term "cycloalkyl" means a cyclic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The symbol "-" means a bond.

The term "patient" means all animals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, and pigs.

15 The term "substituted" means that the base organic radical has one or more substituents. For example, substituted cyclohexyl means a cyclohexyl radical that has one or more substituents. Substituents include, but are not limited to, halogen, C₁-C₈ alkyl, -CN, -CF₃, -NO₂, -NH₂, -NHC₁-C₈ alkyl,

20 $\begin{array}{c} \text{O} \\ || \\ -\text{SC}_1-\text{C}_6 \text{ alkyl}, -\text{N}(\text{C}_1-\text{C}_8 \text{ alkyl})_2, -\text{OC}_1-\text{C}_8 \text{ alkyl}, \text{ and } -\text{OH}. \text{ Particularly} \\ || \\ \text{O} \end{array}$

preferred substituents include, but are not limited to tert-butyl, methyl, chlorine, fluorine, bromine, -OCH₃, -OCH₂CH₃, -OH, and -N(CH₃)₂. Also, in the case of

25 substituted aryl, the substituent may comprise $\begin{array}{c} \text{O} - \\ \diagdown \quad \diagup \\ \text{O} - \end{array}$.

The term "cycloalkenyl" means a cycloalkyl group having at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopentene, cyclobutene, and cyclohexene.

30 The term "heterocycle" means a cycloalkyl group wherein one or more carbon atom is replaced with a heteroatom. Examples of heterocycles include, but are not limited to, pyrrolidinyl, piperidinyl, and piperazinyl.

-18-

Those skilled in the art are easily able to identify patients having a stroke or at risk of having a stroke; cerebral ischemia; head trauma; epilepsy; asthma; amyotrophic lateral sclerosis; or pain. For example, patients who are at risk of having a stroke include, but is not limited to patients having hypertension or
5 undergoing major surgery.

A therapeutically effective amount is an amount of a compound of Formula I, that when administered to a patient, ameliorates a symptom of the disease.

The compounds of the present invention can be administered to a patient
10 either alone or a part of a pharmaceutical composition. The compositions can be administered to patients either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

15 Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols
20 (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

25 These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the
30 like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ

-20-

oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

5 Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide,
10 bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body
15 temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any
20 preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters,
25 amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the
30 invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable

-21-

organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C₁-C₆ alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C₅-C₇ cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C₁-C₄ alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C₁-C₆ alkyl amines and secondary C₁-C₆ dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C₁-C₃ alkyl primary amines, and C₁-C₂ dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B.

-22-

Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the present invention can exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisomeric forms of the compounds, as well as mixtures thereof including racemic mixtures, form part of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is preferable.

The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to those skilled in the art.

In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as through metabolism.

The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any way.

The following abbreviations are used throughout this application:

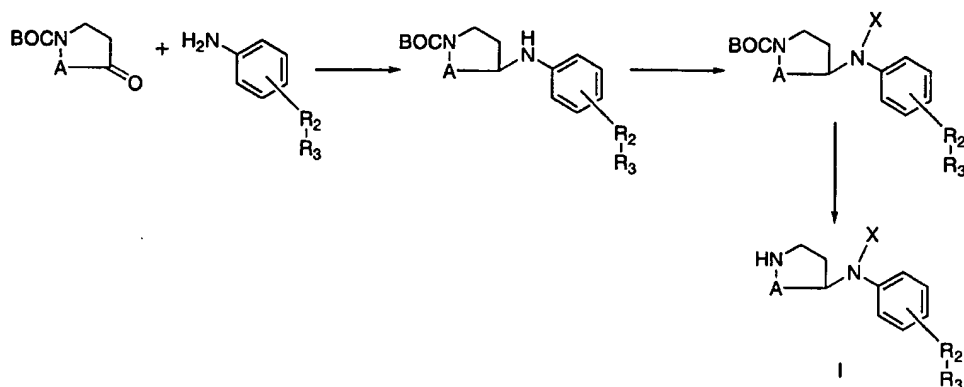
Pr	propyl
Et	ethyl
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophosphate
Bz or Bn	benzyl
TFA	trifluoroacetic acid

-23-

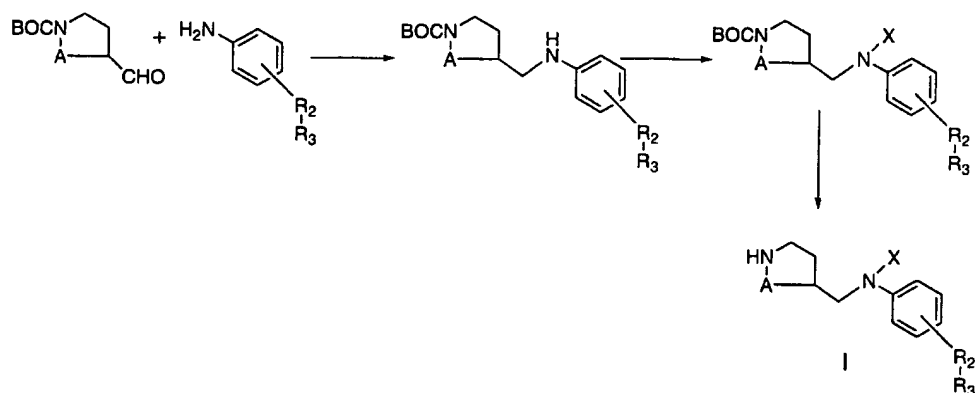
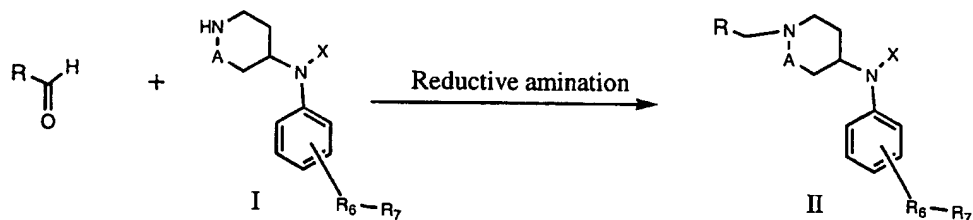
APCI	atmospheric pressure chemical ionization
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
HPLC	high pressure liquid chromatography
DMF	dimethyl formamide
EtOAc	ethyl acetate
EtOH	ethanol
MS	mass spectrum
DCM	dichloromethane
Et ₃ N	triethyl amine
THF	tetrahydrofuran
IR	infrared
Oac	acetate
bu	butyl
iso-pr	iso-propyl
Fmoc	9-fluorenylmethyloxycarbonyl
BOC	tertiary butyloxycarbonyl

General Procedure for the Preparation of Calcium Channel Blockers (II):

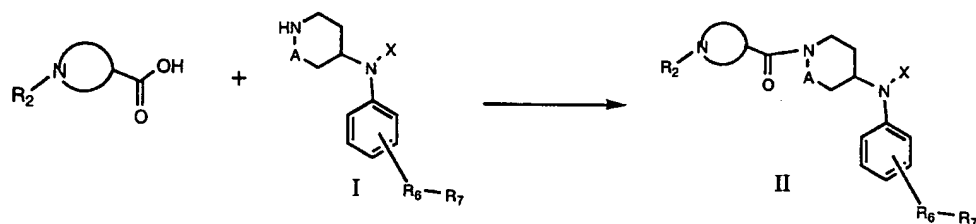
Schemes III -VI below illustrates the preparation of the title compounds II. The preparation of intermediates I are illustrated in Schemes I and II.

5 Step I: The preparation of intermediate I**Scheme I**

-24-

Step II: The preparation of the title compounds IIScheme II

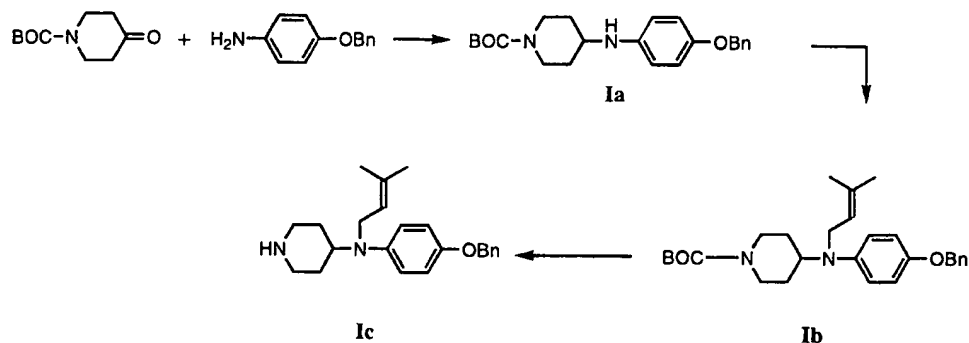
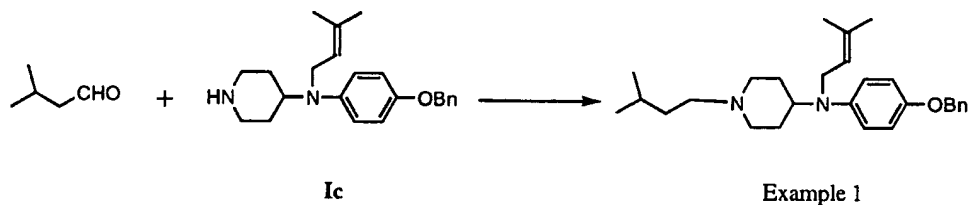
5

Scheme IIIEXAMPLE 1

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-
amine

10

-25-

Scheme IVScheme V

- 5 Step 1: The preparation of 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (Ia): 4-Benzyloxyaniline hydrochloride salt (10 g, 42.4 mmol) was suspended in EtOAc (500 mL) and washed three times with saturated sodium bicarbonate solution, once with brine, dried over Na₂SO₄, and concentrated. The free base was dissolved in CH₂Cl₂ (250 mL), treated with 1-tert-butyl-carbonyl-
- 10 4-piperidone (8.45 g, 42.4 mmol), stirred for thirty minutes and then cooled to 0°C. NaBH(OAc)₃ (13.5 g, 63.6 mmol) was added and the reaction was allowed to warm to room temperature and stir for eighteen hours. The reaction was diluted with CH₂Cl₂ (250 mL), washed with saturated sodium bicarbonate solution and brine, dried over Na₂SO₄, and concentrated to give 15.3 g (94%) of the desired product.
- 15 MS: 383 (M+1 for C₂₃H₃₀N₂O₃); TLC: SiO₂, R_f 0.39 (2:1 hexane/EtOAc).

- Step 2: The preparation of 4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-aminol]-piperidine-1-carboxylic acid tert-butyl ester (Ib): 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (5.0 g, 13.1 mmol) was dissolved in THF (65 mL), then treated with N,N-diisopropylethylamine (9.1 mL,
- 20

-26-

52.4 mmol) and 4-bromo-2-methyl-2-butene (3.0 mL, 26.2 mmol). The reaction was heated to 40°C for eighteen hours, then concentrated in vacuo. The residue was chromatographed on silica gel eluting with 5:1 hexane/EtOAc to give 5.15 g of the desired compound. (87% yield)

5 MS: 451 (M+1 for C₂₈H₃₈N₂O₃); TLC: SiO₂, R_f 0.26 (5:1 hexane/EtOAc); Analysis (C₂₈H₃₈N₂O₃): (Calc) C: 74.63, H: 8.50, N: 6.22 (found) C: 74.42, H: 8.50, N: 6.22.

Step 3: The preparation of (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine, (Ic): 4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-

10 piperidine-1-carboxylic acid tert-butyl ester (5.0 g, 11.1 mmol) was dissolved in CH₂Cl₂ (20 mL) and treated with TFA (20 mL). The reaction was stirred for ten minutes, then concentrated in vacuo. The residue was redissolved in EtOAc (400 mL), then washed with saturated bicarbonate solution (2x400 mL) and brine (1x400 mL), dried over Na₂SO₄, and concentrated in vacuo to give 3.9 g (99%)
15 of the desired product as a pale oil.

MS: 351 (M+1 for C₂₃H₃₀N₂O₁); TLC: SiO₂, R_f 0.49 (10% MeOH/CH₂Cl₂).

Step 4: The preparation of Example 1. (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine: (4-Benzyloxy-phenyl)-(3-

20 methyl-but-2-enyl)-piperidin-4-yl-amine (0.2 g, 0.57 mmol) was dissolved in dichloromethane and treated with isovaleraldehyde (61 µL, 0.57 mmol). The reaction was stirred for thirty minutes, then cooled to 0°C in an ice bath and treated with NaBH(OAc)₃ (0.18 g, 0.86 mmol). The reaction was allowed to warm to room temperature as the ice melted and stirred for eighteen hours at room temperature. The reaction was diluted with EtOAc (125 mL), then washed with
25 saturated bicarbonate (125 mL) and brine (125 mL), dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluting with 7% MeOH/CH₂Cl₂ to give 0.17 g of the title compound. Yield: 71%.

MS: 421 (M+1 for C₂₈H₄₀N₂O₁); mp: 170°C dec.; TLC: SiO₂, R_f 0.22 (5% MeOH/CH₂Cl₂); Analysis (C₂₈H₄₀N₂O₁·0.25H₂O) (Cal.) C: 79.10, H: 9.60, N:
30 6.59 (found) C: 78.83, H: 9.46, N: 6.67.

-27-

EXAMPLE 2

(4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was made in accordance with the process of Example 1 (Step 4), except that 3,3-dimethylbutyraldehyde was used instead of isovaleraldehyde.

5 Yield: 54%

MS: 435 (M+ for $C_{29}H_{42}N_2O_1$); an oil; TLC: $R_f = 0.2$ (SiO_2 , EtOAc/Hexanes);

Analysis ($C_{29}H_{42}N_2O_1$): (Cal.) C: 80.13, H 9.74, N: 6.45, (found) C: 79.82, H: 9.92, N: 6.28.

EXAMPLE 3

10 (4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was made in accordance with the process of Example 1 (Step 4), except that 4-tert-butyl-benzaldehyde was used instead of isovaleraldehyde. Yield 76%.

MS: 497 (M+1 for $C_{34}H_{44}N_2O_1$); sticky solid; TLC: SiO_2 , R_f 0.38 (8% MeOH/

15 CH_2Cl_2);

Analysis ($C_{34}H_{44}N_2O_1$): (Cal.) C: 82.21, H: 8.93, N: 5.64 (found) C: 81.99, H: 9.02, N: 5.29.

EXAMPLE 4

20 (4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was made in accordance with the process of Example 1 (Step 4), except that 4-bromobenzaldehyde was used instead of isovaleraldehyde. Yield: 40%

MS: 521 (M+ for $C_{30}H_{35}N_2O_1Br_1$); an oil; TLC: SiO_2 , $R_f = 0.8$ (50% EtOAc/Hexanes);

25 Analysis ($C_{30}H_{35}N_2O_1Br_1 \cdot H_2O$): (Cal.) C: 67.03, H:6.94, N: 5.21, (found) C: 67.03, H:6.62, N: 4.82.

-28-

EXAMPLE 5

4-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-ylmethyl}-phenol was made in accordance with the process of Example 1 (Step 4), except that 4-hydroxybenzaldehyde was used instead of isovaleraldehyde. Yield: 31%.
5 MS: 457 (M+1 for $C_{30}H_{36}N_2O_2$); sticky solid; TLC: SiO_2 , R_f 0.55 (10% MeOH/ CH_2Cl_2);
Analysis ($C_{30}H_{36}N_2O_2 \cdot 0.25H_2O$) (Cal.) C: 78.14, H: 7.98, N: 6.08 (found) C: 78.39, H: 7.70, N: 6.00.

EXAMPLE 6

10 (4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was made in accordance with the process of Example 1 (Step 4), except that 4-dimethylaminobenzaldehyde was used instead of isovaleraldehyde. Yield: 18%.
MS: 484 (M+1 for $C_{32}H_{41}N_3O_1$); sticky solid; TLC: SiO_2 , R_f 0.35 (6%
15 MeOH/ CH_2Cl_2);
Analysis ($C_{32}H_{41}N_3O_1 \cdot 0.25H_2O$): (Cal.) C: 78.72, H: 8.57, N: 8.61 (found) C: 78.98, H: 8.61, N: 8.59.

EXAMPLE 7

20 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine was made in accordance with the process of Example 1 (Step 4), except that pyrrole-2-carboxaldehyde was used instead of isovaleraldehyde.
MS: 430 (M+1 for $C_{28}H_{35}N_3O_1$); sticky solid; TLC: SiO_2 , R_f 0.42 (8% MeOH/ CH_2Cl_2);
25 HPLC: 100% pure, RT = 3.09 min. (C-18 column, 1:1 CH_3CN/H_2O with 0.5% TFA, 0.75 mL/min).

EXAMPLE 8

(4-Benzyloxy-phenyl)-[1-(1H-imidazol-4-ylmethyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was made in accordance with the process of Example 1

-29-

(Step 4), except that 4-formylimidazole was used instead of isovaleraldehyde.

Yield: 53%

MS: 431 (M+ for $C_{27}H_{34}N_4O_1$); sticky solid; TLC: SiO_2 R_f = 0.2 (10%

MeOH/ CH_2Cl_2);

5 Analysis ($C_{27}H_{34}N_4O_1 \cdot H_2O$): (Cal.) C: 72.29, H: 8.09, N: 12.49, (found) C: 72.07, H: 7.87, N: 12.17.

EXAMPLE 9

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pyridin-2-ylmethyl-piperidin-4-yl)-amine was made in accordance with the process of Example 1 (Step 4), except
10 that pyridine-2-carboxaldehyde was used instead of isovaleraldehyde. Yield: 66%.
MS: 442 (M+1 for $C_{29}H_{35}N_3O_1$); mp 132-134°C; TLC: SiO_2 , R_f 0.18 (5%
MeOH/ CH_2Cl_2);
Analysis ($C_{29}H_{35}N_3O_1$): (Calc.) C: 78.87, H: 7.99, N: 9.51 (found) C: 78.55, H: 8.17, N: 9.43.

15

EXAMPLE 10

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-amine was made in accordance with the process of Example 1 (Step 4), except that tetrahydropyran-4-one was used instead of isovaleraldehyde. Yield:
41%.
20 MS: 435 (M+1 for $C_{28}H_{38}N_2O_2$); sticky solid; TLC: SiO_2 , R_f 0.29 (5%
MeOH/ CH_2Cl_2);
HPLC: 100% pure, RT = 3.34 min. (C-18 column, 1:1 CH_3CN/H_2O with 0.5%
TFA, 0.75 mL/min).

EXAMPLE 11

25 {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-2-yl]-methanone

Step 1: The preparation of piperidine-2-carboxylic acid: Pyridine-2-carboxylic acid (10.0 g, 81.3 mmol) was treated with H_2O (100 mL), NH_4OH (10 mL), and

-30-

20% Pd/C (2.0 g) and shaken under an atmosphere of H₂. The reaction was filtered and concentrated to give 10 g (95%) of the desired product.

MS: 130 (M+1 for C₆H₁₁N₁O₂).

Step 2: The preparation of 1-(3-methyl-butyl)-piperidine-2-carboxylic acid:

5 Piperidine-2-carboxylic acid (4.0 g, 30 mmol) was treated with EtOH (100 mL), isovaleraldehyde (6.6 mL, 60 mmol), and 20% Pd/C (1.0 g) and shaken under an atmosphere of H₂ for twenty-three hours. The reaction was filtered and concentrated to dryness, then twice stirred with acetone (100 mL) for 1 hour and filtered. The solid was dried under vacuum to give 5.0 g of the desired product.

10 MS: 200 (M+1 for C₁₁H₂₁N₁O₂); mp 230-231°C;

Analysis (calc) C: 66.29, H: 10.62, N: 7.03 (found) C: 66.07, H: 10.23, N: 6.84.

Step 3: The preparation of Example 11: {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-2-yl]-methanone:

15 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (0.175 g, 0.50 mmol) was dissolved in DMF (5 mL). Diisopropylethylamine (0.26 mL, 1.5 mmol) and N-isopentylpiperidine-2-carboxylic acid (0.1 g, 0.50 mmol) were added, followed by HBTU (0.19 g, 0.50 mmol). The reaction was stirred for 5 hours at room temperature, then diluted with EtOAc (125 mL), washed with saturated sodium bicarbonate solution and brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluting with 4% MeOH/CH₂Cl₂ to give 91 mg (34%) of the title compound.

MS: 532 (M+1 for C₃₄H₄₉N₃O₂); sticky solid; TLC: SiO₂, R_f 0.49 (6% MeOH/CH₂Cl₂);

25 Analysis (C₃₄H₄₉N₃O₂·0.25H₂O) (Cal.) C: 76.15, H: 9.30, N: 7.84 (found) C: 76.00, H: 9.31, N: 7.87.

EXAMPLE 12

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-3-yl]-methanone

-31-

Step 1: The preparation of 1-(3-Methyl-butyl)-piperidine-3-carboxylic acid:

Piperidine-3-carboxylic acid (19.8 g, 153 mmol) was treated with EtOH (400 mL), isovaleraldehyde (33 mL, 307 mmol), and 20% Pd/C (2.0 g). The reaction was shaken under H₂, then filtered and concentrated to dryness and further dried in vacuo. The crude material was treated with acetone, stirred, and filtered three times. The solid obtained was dried in vacuo to give 22.0 g (72%) of the desired product.

MS: 200 (M+1 for C₁₁H₂₁N₁O₂);

Step 2: The preparation of Example 12: {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-3-yl]-methanone was made in accordance with the process of Example 11 (Step 3), except 1-(3-Methyl-butyl)-piperidine-3-carboxylic acid was used instead of 1-(3-Methyl-butyl)-piperidine-2-carboxylic acid.

MS: 532 (M+1 for C₃₄H₄₉N₃O₂); sticky solid; TLC: SiO₂, R_f 0.3 (20%

MeOH/CH₂Cl₂);

Analysis (C₃₄H₄₉N₃O₂·0.5H₂O) (Cal.) C: 75.52, H: 9.32, N: 7.70 (found) C: 75.62, H: 9.25, N: 7.91.

EXAMPLE 13

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-4-yl]-methanone

Step 1: The preparation of 1-(3-Methyl-butyl)-piperidine-4-carboxylic acid:

Piperidine-4-carboxylic acid (10.0 g, 77.4 mmol) was dissolved in EtOH (400 mL) and treated with isovaleraldehyde (17 mL, 155 mmol) and 20% Pd/C (1.0 g). The reaction mixture was shaken under an atmosphere of H₂ (50 psi) for twenty hours. The reaction was filtered through Celite and concentrated in vacuo to give 15.75 g (97%) of the desired product as a white solid.

MS: 200 (M+1 for C₁₁H₂₁N₁O₂).

-32-

- Step 2: The preparation of Example 13: 1-(3-Methyl-butyl)-piperidine-4-carboxylic acid (0.1 g, 0.50 mmol) was dissolved in DMF (5 mL) and treated with (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (0.175 g, 0.50 mmol), diisopropylethylamine (0.26 mL, 1.5 mmol), and HBTU (0.19 g, 0.50 mmol). The reaction was stirred for 4 hours, then diluted with EtOAc (125 mL), washed with saturated sodium bicarbonate solution and brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluting with 8% MeOH/CH₂Cl₂ to give 47 mg (18%) of {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-4-yl]-methanone.
- MS: (M+1 for C₃₄H₄₉N₃O₂); sticky solid; TLC: SiO₂, R_f 0.32 (8% MeOH/CH₂Cl₂);
- HPLC: 97% pure, RT = 6.12 min (C-18 column, gradient over ten minutes: 10:90 to 98:2 CH₃CN/H₂O with 0.1% formic acid, 1.0 mL/min).

EXAMPLE 14

- {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone

- Step 1: The preparation of piperazine-2-carboxylic acid: Pyrazine-2-carboxylic acid (102.7 g, 0.827 mol) was dissolved in H₂O (600 mL), treated with NaOH (66 g, 1.65 mol) and 20% Pd/C (5.0 g), and hydrogenated for fifteen hours. The reaction was filtered and concentrated. Concentrated HCl was added to the solution and a white precipitate formed. The solid was washed with cold H₂O, collected by filtration and dried in vacuo to give 137.2 g (99.6%) of the desired product as the HCl salt.
- MS: 131 (M+1 for C₅H₁₀N₂O₂).

- Step 2: The preparation of piperazine-1,2,4-tricarboxylic acid 1-benzyl ester 4-tert-butyl ester: Piperazine-2-carboxylic acid (37.5 g, 185 mmol) was dissolved in H₂O (600 mL) and dioxane (600 mL). The solution was adjusted to pH 11 by the addition of 50% NaOH. 2-(t-butoxycarbonyloxymino)-2-phenylacetonitrile (51.0 g, 210 mmol) in dioxane (300 mL) was added portionwise. The reaction was

-33-

maintained at pH 11 by the addition of 50% NaOH over 3 hours, then cooled to 0°C in an ice bath and adjusted to pH 9.5 with 6 N HCl. To the cooled solution was added benzylchloroformate dropwise while maintaining the pH at 9.5. The reaction was allowed to warm to room temperature and stir for 2.5 days. The reaction was extracted with Et₂O (4x250 mL), then the aqueous layer was acidified to pH 2 with concentrated HCl and extracted with EtOAc (4x250 mL). The EtOAc layer was dried over MgSO₄ and concentrated to give 64.2 g (95%) of the desired product.

MS: 365 (M+1 for C₁₈H₂₄N₂O₆).

Step 3: The preparation of piperazine-1,2,4-tricarboxylic acid, 4-(1,1-dimethylethyl) 2-methyl 1-(phenylmethyl) ester: Piperazine-1,2,4-tricarboxylic acid 1-benzyl ester 4-tert-butyl ester (20.7 g, 56.9 mmol) was dissolved in THF (100 mL) and cooled. A solution of diazomethane in Et₂O was added until a yellow color persisted. The reaction was quenched with acetic acid and concentrated. The residue was dissolved in heptane/toluene (1:1) and gave 12.0 g of the desired product on overnight standing.

MS: 379 (M+1 for C₁₉H₂₆N₂O₆); mp: 85-86°C; TLC: R_f 0.26 (1:1 Et₂O/heptane); Analysis (calc) C: 60.31, H: 6.93, N: 7.40 (found) C: 60.58, H: 6.99, N: 7.43.

Step 4: The preparation of piperazine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester: Piperazine-1,2,4-tricarboxylic acid, 4-(1,1-dimethylethyl) 2-methyl 1-(phenylmethyl) ester (9.0 g, 23.8 mmol) was treated with MeOH (100 mL) and 20% Pd/C (1.0 g) and shaken under an atmosphere of H₂. The reaction was filtered and concentrated to give 6.0 g (99%) of the desired product.

MS: 245 (M+1 for C₁₁H₂₀N₂O₄).

Step 5: The preparation of 4-(3-Methyl-butyl)-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester: Piperazine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (6.0 g, 24.6 mmol) was treated with EtOH (100 mL), isovaleraldehyde (5.3 mL, 50 mmol), and 20% Pd/C (1.0 g), then shaken under an

-34-

atmosphere of H₂. The reaction was filtered and concentrated. The residue was chromatographed on silica gel eluting with 2:1 hexanes/EtOAc to give 7.0 g (90%) of the desired product as an oil.

MS: 316 (M+1 for C₁₆H₃₀N₂O₄); colorless liquid; TLC: SiO₂, R_f 0.8 (50% hexanes/EtOAc);

Analysis: (C₁₆H₃₀N₂O₄) (calc.) C: 61.12, H: 9.62, N: 8.91; (found) C: 61.00, H: 9.54, N: 8.54.

Step 6: The preparation of 1-(3-Methyl-butyl)-piperazine-2-carboxylic acid methyl ester: 4-(3-Methyl-butyl)-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl (5.89 g, 18.4 mmol) was dissolved in CH₂Cl₂ (35 mL) and treated with TFA (35 mL). The reaction was stirred for 30 minutes, then concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with saturated sodium bicarbonate solution, dried over powdered sodium bicarbonate, and concentrated to give 4.3 g of the desired product.

MS: 215 (M+1 for C₁₁H₂₂N₂O₂); colorless liquid; TLC: SiO₂, R_f 0.4 (5% MeOH/EtOAc).

Step 7: The preparation of 4-Methyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid methyl ester: 1-(3-Methyl-butyl)-piperazine-2-carboxylic acid methyl ester (1.5 g, 7 mmol) was dissolved in MeOH (50 mL), treated with 37% HCHO (1.7 g, 14 mmol), and 10% Pd/C (0.3 g), and shaken under an atmosphere of H₂. The reaction was filtered and concentrated. The residue was chromatographed on silica gel eluting with 20:1 EtOAc/MeOH to give 1.3 g (81%) of the desired product. MS: 229 (M+1 for C₁₂H₂₄N₂O₂); colorless liquid; ; TLC: SiO₂, R_f 0.3 (5% MeOH/EtOAc).

Step 8: The preparation of 4-Methyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid: 4-Methyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid methyl ester (1.0 g, 4.4 mmol) was treated with acetone (20 mL), water (14 mL), and concentrated HCl (6 mL), and refluxed for 34 hours. The reaction was concentrated to give 0.9 g (95%) of the desired product.

-35-

MS: 215 (M+1 for $C_{11}H_{22}N_2O_2$).

Step 9: The preparation of Example 14: Example 14 was made in accordance with the process of Example 11 (Step 3), except that 4-Methyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid was used instead of 1-(3-Methyl-butyl)-piperidine-2-carboxylic acid.

MS: 547 (M+1 for $C_{34}H_{50}N_4O_2$); sticky solid; TLC: SiO_2 , R_f 0.3 (20% MeOH/ CH_2Cl_2);

Analysis ($C_{34}H_{50}N_4O_2$) (Cal.) C: 74.68, H: 9.22, N: 10.25 (found) C: 74.34, H: 9.16, N: 10.00.

10

EXAMPLE 15

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone

Step 1: The preparation of 4-Isopropyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid methyl ester: The compound was prepared in accordance with the process of Steps 1-3 in Example 14, except that acetone was used instead of formaldehyde in Step 3.

MS: 257 (M+1 for $C_{14}H_{28}N_2O_2$); oil; TLC: SiO_2 , R_f 0.5 (5% MeOH/EtOAc).

Step 2: The preparation of 4-Isopropyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid: The compound was made in accordance with the process of Step 4 in Example 14, except that 4-Isopropyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid methyl ester was used instead of 4-Methyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid methyl ester.

MS: 243 (M+1 for $C_{13}H_{26}N_2O_2$).

Step 3: The preparation of Example 15: {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone is made in accordance with the process of Example 11 (Step 3), except that 4-Isopropyl-1-(3-methyl-butyl)-piperazine-2-carboxylic acid was used instead of 1-(3-Methyl-butyl)-piperidine-2-carboxylic acid.

-36-

MS: 575 (M+1 for $C_{36}H_{54}N_4O_2$); sticky solid; TLC: SiO_2 , R_f 0.2 (20% MeOH/ CH_2Cl_2);

Analysis ($C_{36}H_{54}N_4O_2 \cdot 0.5H_2O$) (Cal.) C: 74.06, H: 9.51, N: 9.60 (found) C: 73.90, H: 9.37, N: 9.87.

5

EXAMPLE 16

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[6-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone

Step 1: The preparation of 6-Methyl-piperidine-2-carboxylic acid: The compound was made in accordance with the process in Example 11 (Step 1), except that 6-methyl-pyridine-2-carboxylic acid was used instead of pyridine-2-carboxylic acid.
MS: 140 (M+1 for $C_7H_7N_1O_2$).

Step 2: The preparation of 6-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid: The compound was made in accordance with the process in of Step 2 in Example 11, except that 6-Methyl-piperidine-2-carboxylic acid was used instead of piperidine-2-carboxylic acid.
MS: 214 (M+1 for $C_{12}H_{23}N_1O_2$).

Step 3: The preparation of Example 16: {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[6-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone was made in accordance with the process in Step 3 in Example 11, except that 6-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid was used instead of 1-(3-Methyl-butyl)-piperidine-2-carboxylic acid. The final product was further prepared as a HCl salt.
MS: 546 (M+1 for $C_{35}H_{51}N_3O_2$); mp 184-188°C; TLC: SiO_2 , R_f 0.5 (10% MeOH/ CH_2Cl_2) for the free base.

25

EXAMPLE 17

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone

-37-

Step 1. The preparation of 4-methyl-2-cyano-pyridine: 4-Picoline-N-oxide (10.0 g, 91.6 mmol) was dissolved in CH_2Cl_2 (92 mL) and dried over MgSO_4 . The drying agent was filtered away and the solution was added to trimethylsilyl cyanide (11.5 g, 116 mmol). A solution of dimethylcarbamoyl chloride (12.5 g, 116 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 45 minutes. The reaction was stirred overnight. A 10% solution of K_2CO_3 in water (100 mL) was added dropwise and stirred for ten minutes. The layers were separated, then the aqueous layer was washed with CH_2Cl_2 (2x100 mL). The organic layers were combined, dried over Na_2SO_4 , and concentrated to give the desired product (13.18 g crude material).

MS: 119 ($\text{M}+1$ for $\text{C}_7\text{H}_6\text{N}_2$); ^1H NMR (CDCl_3) δ 2.28 (s, 3 H), 7.18 (d, 1 H, $J = 4.9$ Hz), 7.37 (s, 1 H), 8.41 (d, 1 H, $J = 5.1$ Hz).

Step 2. The preparation of 4-methyl-pyridine-2-carboxylic acid: 4-Methyl-2-cyano-pyridine (13.0 g, 110 mmol) was treated with 6N HCl and heated to reflux for twenty hours. The reaction was concentrated to give the desired product.

MS: 138 ($\text{M}+1$ for $\text{C}_8\text{H}_{11}\text{N}_1\text{O}_2$); ^1H NMR ($\text{DMSO}-d_6$) δ 2.43 (s, 3 H), 7.61 (dd, 1 H, $J = 5.4, 1.0$ Hz), 7.99 (d, 1 H, $J = 1.0$ Hz), (8.57 (d, 1 H, $J = 5.4$ Hz).

Step 3. The preparation of 4-methyl-pyridine-2-carboxylic acid methyl ester: 4-Methyl-pyridine-2-carboxylic acid (4.39 g, 25.3 mmol) was suspended in THF. A solution of diazomethane (60 mL, 0.43 M) in THF was added dropwise and the reaction was stirred for three hours. Several drops of AcOH were added to quench the reaction, then saturated bicarbonate solution was added. The reaction was diluted with EtOAc and the layers were separated. The aqueous layer was washed twice with EtOAc and the organic layers were combined, dried over Na_2SO_4 , and concentrated. The residue was chromatographed on silica gel eluting with 4% MeOH/ CH_2Cl_2 to give 1.17 g (31%) of the desired product as an oil.

MS: 152 ($\text{M}+1$ for $\text{C}_8\text{H}_9\text{N}_1\text{O}_2$); ^1H NMR (CDCl_3) δ 2.40 (s, 3 H), 3.97 (s, 3 H), 7.26 (d, 1 H, $J = 4.2$ Hz), 7.94 (s, 1 H), 8.56 (d, 1 H, $J = 4.9$ Hz).

-38-

Step 4. The preparation of 4-methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid methyl ester: 4-Methyl-pyridine-2-carboxylic acid methyl ester (1.17 g, 7.74 mmol) was dissolved in acetic acid (50 mL), treated with PtO_2 (0.5 g), and shaken under an atmosphere of H_2 (50 psi) for thirty hours. The reaction mixture was
5 evaporated under reduced pressure, then redissolved in EtOH (50 mL), treated with isovaleraldehyde (0.5 mL, 15 mmol) and 20% Pd/C (0.2 g), and shaken under H_2 (50 psi) for twenty hours. The reaction was filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 10% MeOH/ CH_2Cl_2 to give 1.36 g (77%) of the desired product.
10 MS: 228 (M+1 for $\text{C}_{13}\text{H}_{15}\text{N}_1\text{O}_2$).

Step 5. The preparation of 4-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid: 4-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid methyl ester (1.36 g, 5.98 mmol) was dissolved in a mixture acetone (40 mL) and water (28 mL), treated with concentrated HCl (12 mL) and heated to 95°C overnight.
15 Another 5 mL of concentrated HCl was added and the reaction was heated for another seventy-two hours. The reaction was cooled to room temperature and concentrated in vacuo to give 1.18 g (93%) of the desired product.
MS: 214 (M+1 for $\text{C}_{12}\text{H}_{23}\text{N}_1\text{O}_2$).

Step 6: The preparation of Example 17: {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone was made in accordance with the process of Example 11 (Step 3), except that 4-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid was used instead of 1-(3-Methyl-butyl)-piperidine-2-carboxylic acid (14% yield).
20 MS: 546 (M+1 for $\text{C}_{35}\text{H}_{51}\text{N}_3\text{O}_2$); sticky solid; TLC: SiO_2 , R_f 0.45 (7% MeOH/ CH_2Cl_2);
25 HPLC: 100% pure, RT = 6.73 min. (C-18 column, gradient over 10 min.: 10:90 to 98:2 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ with 0.1 % formic acid, 1.0 mL/min).

-39-

EXAMPLE 18

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[3-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone

5 Step 1: 3-methyl-piperidine-2-carboxylic acid was prepared by the method of Step 1 in Example 11, except that 3-methyl-pyridine-2-carboxylic acid was used instead of pyridine-2-carboxylic acid.

MS: 144 (M+1 for $C_7H_{13}N_1O_2$).

10 Step 2: 3-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid was prepared by the method of Step 2 in Example 11, except that 3-methyl-piperidine-2-carboxylic acid was used instead of piperidine-2-carboxylic acid.

MS: 214 (M+1 for $C_{12}H_{23}N_1O_2$); a solid.

15 Step 3: The preparation of Example 18: {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[3-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone was made in accordance with the process of Example 11 (Step 3), except that 3-Methyl-1-(3-methyl-butyl)-piperidine-2-carboxylic acid was used instead 1-(3-Methyl-butyl)-piperidine-2-carboxylic acid. The final product was further prepared as a HCl salt.

MS: 546 (M+1 for $C_{35}H_{51}N_3O_2$); mp 176-180°C; TLC: SiO_2 , R_f 0.2 (10% MeOH/ CH_2Cl_2) for the free base;

20 Analysis ($C_{35}H_{51}N_3O_2 \cdot 2HCl \cdot 2.5H_2O$) (Cal.) C: 63.34, H: 8.80, N: 6.33 (found) C: 63.29, H: 8.71, N: 6.01.

EXAMPLE 19

25 (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Example 1 (Steps 1-4), except that benzaldehyde was used instead of isovaleraldehyde in Step 4.

MS: 441.3 (M+1 for $C_{30}H_{36}N_2O_1$); an oil; TLC: SiO_2 , R_f 0.21 (3:1 hexanes/EtOAc);

-40-

Analysis ($C_{30}H_{36}N_2O_1$); (Calc) C: 81.78, H: 8.24, N: 6.36, (found) C: 81.77, H: 8.24, N: 6.35.

EXAMPLE 20

5 4-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-butan-2-ol was prepared in accordance with the methods of Example 1 (Steps 1-4), except that 3-hydroxybutyraldehyde was used instead of isovaleraldehyde in Step 4.

MS: 423 (M+1 for $C_{27}H_{38}N_2O_2$); an oil; TLC: SiO_2 , R_f 0.20 (9:1 EtOAc/MeOH);

10 Analysis ($C_{27}H_{38}N_2O_2 \cdot 0.25H_2O$); (calc) C: 75.93, H: 9.10, N: 6.63, (found) C: 76.05, H: 9.08, N: 6.38.

EXAMPLE 21

15 4-{4-[(4-Benzyloxy-phenyl)-(1-furan-2-ylmethyl-piperidin-4-yl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Example 1 (Steps 1-4), except that furan-2-carboxaldehyde was used instead of isovaleraldehyde in Step 4.

MS: 431 (M+1 for $C_{28}H_{34}N_2O_2$); an oil; TLC: SiO_2 , R_f 0.20 (1:1 hexanes/EtOAc);

20 Analysis ($C_{28}H_{34}N_2O_2$); (calc) C: 78.01, H: 7.90, N: 6.51, (found) C: 77.95, H: 8.03, N: 6.43.

EXAMPLE 22

25 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-phenyl-propyl)-piperidin-4-yl]-amine was prepared in accordance with the methods of Example 1 (Steps 1-4), except that 3-phenylpropionaldehyde was used instead of isovaleraldehyde in Step 4.

MS: 469.3 (M+1 for $C_{32}H_{40}N_2O_1$); an oil; TLC: SiO_2 , R_f 0.32 (1:9 EtOAc/Hexane);

Analysis ($C_{32}H_{40}N_2O_1$); (calc) C: 82.01, H: 8.60, N: 5.98, (found) C: 82.02, H: 8.36, N: 5.86.

-41-

EXAMPLE 23

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-phenethyl-piperidin-4-yl)-amine was prepared in accordance with the methods of Example 1 (Steps 1-4), except that phenylacetaldehyde was used instead of isovaleraldehyde in Step 4.

5 MS: 455.2 (M+1 for $C_{31}H_{38}N_2O_1$); an oil; TLC: SiO_2 , R_f 0.40 (1:9 EtOAc/Hexane);
Analysis ($C_{31}H_{38}N_2O_1$); (calc) C: 81.90, H: 8.42, N: 6.16; (found) C: 81.87, H: 8.41, N: 5.91.

EXAMPLE 24

10 (4-Benzyloxy-phenyl)-[1-(4-methanesulfonyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Example 1 (Steps 1-4), except that 4-methylsulfonylbenzaldehyde was used instead of isovaleraldehyde in Step 4.

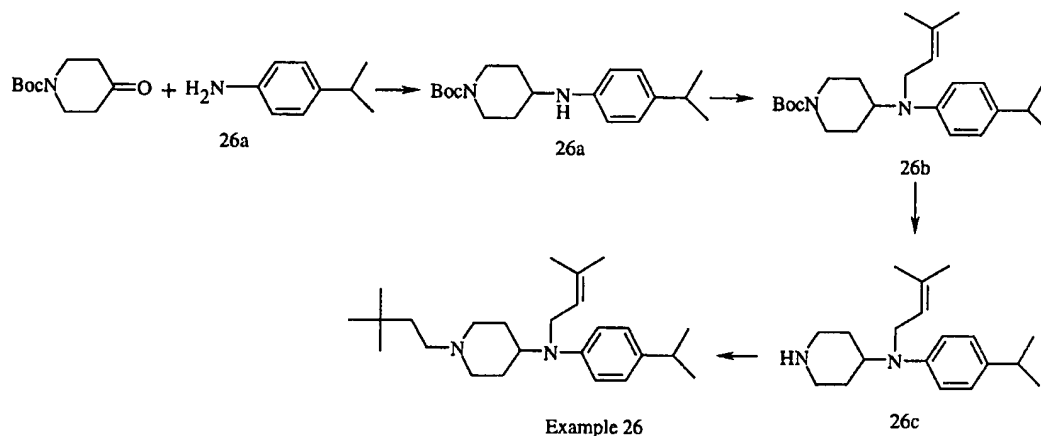
MS: 519.2 (M+1 for $C_{31}H_{38}N_2O_3S_1$); an oil; TLC: SiO_2 , R_f 0.24 (1:9 EtOAc/Hexane);
15 HPLC (C-18 column, 1:1 CH_3CN/H_2O + 0.5% TFA): RT = 3.62 min, 90% pure);
HRMS: (calc) 519.2681, (found) 519.2667.

EXAMPLE 25

20 (4-Benzyloxy-phenyl)-[1-(4-fluoro-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Example 1 (Steps 1-4), except that 4-fluorobenzaldehyde was used instead of isovaleraldehyde in Step 4.

MS: 459.2 (M+1 for $C_{30}H_{35}N_2O_1F_1$); an oil; TLC: SiO_2 , R_f 0.32 (2:1 hexanes/EtOAc);
Analysis ($C_{30}H_{35}N_2O_1F_1$); (calc) C: 78.57, H: 7.69, N: 6.11, (found) C: 78.33,
25 H: 7.67, N: 5.96.

-42-

Scheme VI**EXAMPLE 26**

5 [1-(3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine

Step 1: 4-(4-Isopropyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (26a) was prepared in accordance with the methods of Step 1 in Example 1, except that 4-isopropylaniline was used instead of 4-Benzyloxyaniline hydrochloride salt.

10 MS: 319.3 (M+1 for C₁₉H₃₀N₂O₂); an oil; TLC: SiO₂, R_f 0.57 (10% MeOH/CH₂Cl₂).

15 Step 2: 4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (26b) was prepared in accordance with the methods of Step 2 in Example 1, except that 4-(4-Isopropyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (26a) was used instead of 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (1a). MS: 387.3 (M+1 for C₂₄H₃₈N₂O₂); an oil; TLC: SiO₂, 0.33 (9:1 hexane/EtOAc).

20 Step 3: (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (26c) was prepared in accordance with the methods of Step 3 in Example 1, except that 4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic

-43-

acid tert-butyl ester (**26b**) was used instead of 4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**1b**). MS: 287.2 (M+1 for $C_{19}H_{30}N_2$); an oil; TLC: SiO_2 , R_f 0.20 (10% MeOH/ CH_2Cl_2).

- 5 Step 4: The preparation of Example 26: [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 4 in Example 1, except that (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**26c**) was used instead of (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**1c**) and 3,3-
- 10 dimethylbutyraldehyde was used instead of isovaleraldehyde. MS: 371.2 (M+1 for $C_{25}H_{32}N_2$); an oil; TLC: SiO_2 , R_f 0.45 (10% MeOH/ CH_2Cl_2);
- HPLC (C-18 column, 1:1 CH_3CN/H_2O + 0.5% TFA): RT = 4.317 min, 91% pure.

EXAMPLE 27

- 15 4-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-butan-2-ol was prepared in accordance with the methods of Step 4 in Example 26, except that 3-hydroxybutyraldehyde was used instead of 3,3-
- dimethylbutyraldehyde. MS: 359.2 (M+1 for $C_{23}H_{38}N_2O$); an oil; TLC: SiO_2 , R_f 0.47 (10% MeOH/ CH_2Cl_2);
- 20 Analysis ($C_{23}H_{38}N_2O$); (calc) C: 77.04, H: 10.68, N: 7.81, (found) C: 77.40, H: 10.78, N: 7.80.

EXAMPLE 28

- (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-
- 25 amine was prepared in accordance with the methods of Step 4 in Example 26, except that isovaleraldehyde was used instead of 3,3-dimethylbutyraldehyde. MS: 357.3 (M+1 for $C_{24}H_{40}N_2$); an oil; TLC: SiO_2 , R_f 0.50 (10% MeOH/ CH_2Cl_2);

-44-

HPLC (C-18 column, 1:1 CH₃CN/H₂O + 0.5% TFA): RT = 3.737 min, 92% pure.

EXAMPLE 29

[1-(4-Fluoro-benzyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 4 in Example 26,
5 except that 4-fluorobenzaldehyde was used instead of 3,3-dimethylbutyraldehyde.

MS: 395.6 (M+1 for C₂₆H₃₅N₂F); an oil; TLC: SiO₂, R_f 0.71 (10% MeOH/CH₂Cl₂);

Analysis (C₂₆H₃₅N₂F); (calc) C: 79.14, H: 8.94, N: 7.10, (found) C: 79.27, H: 8.86, N: 6.95.

10 HPLC (C-18 column, 1:1 CH₃CN/H₂O + 0.5% TFA): RT = 3.938 min, 97% pure.

EXAMPLE 30

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-(1-pyridin-3-ylmethyl-piperidin-4-yl)-amine was prepared in accordance with the methods of Step 4 in Example 26,
15 except that pyridine-3-carboxaldehyde was used instead of 3,3-dimethylbutyraldehyde.

MS: 378.2 (M+1 for C₂₅H₃₃N₃); an oil; TLC: SiO₂, R_f 0.58 (10% MeOH/CH₂Cl₂);

HPLC (C-18 column, 1:1 CH₃CN/H₂O + 0.5% TFA): RT = 2.095 min, 99% pure.

EXAMPLE 31

20 [1-(1H-Imidazol-4-ylmethyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 4 in Example 26, except that imidazole-4-carboxaldehyde was used instead of 3,3-dimethylbutyraldehyde.

MS: 367.2 (M+1 for C₂₃H₃₄N₄); an oil; TLC: SiO₂, R_f 0.20 (5% MeOH/CH₂Cl₂);
25

HPLC (C-18 column, 1:1 CH₃CN/H₂O + 0.5% TFA): RT = 2.32 min, 85% pure.

EXAMPLE 32

2-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-propan-1-ol was prepared in accordance with the methods of Step 4 in Example 26, except that hydroxyacetone was used instead of 3,3-dimethylbutyraldehyde.

5 MS: 345.3 (M+1 for $C_{22}H_{36}N_2O_1$); an oil; TLC: SiO_2 , R_f 0.36 (6% MeOH/ CH_2Cl_2);

Analysis ($C_{22}H_{36}N_2O_1 \cdot 0.4H_2O$); (calc) C: 75.12, H: 10.54, N: 7.96, (found) C: 75.32, H: 10.33, N: 7.64.

EXAMPLE 33

10 (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine was prepared in accordance with the methods of Step 4 in Example 26, except that pyrrole-2-carboxaldehyde was used instead of 3,3-dimethylbutyraldehyde.

15 MS: 366.2 (M+1 for $C_{24}H_{35}N_3$); an oil; TLC: SiO_2 , R_f 0.18 (4% MeOH/ CH_2Cl_2);

Analysis ($C_{24}H_{35}N_3 \cdot 0.25H_2O$); (calc) C: 77.90, H: 9.67, N: 11.35, (found) C: 77.91, H: 9.66, N: 11.37.

EXAMPLE 34

20 (4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine

Step 1: 4-(4-Isopropoxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**34a**) was prepared in accordance with the methods of Step 1 in Example 1, except that 4-isopropoxyaniline was used instead of 4-Benzyloxyaniline hydrochloride salt.

25 MS: 335.3 (M+1 for $C_{19}H_{30}N_2O_3$); an oil; TLC: SiO_2 , R_f 0.74 (1:1 hexanes/EtOAc).

Step 2: 4-[(4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**34b**) was prepared in accordance with the

-46-

methods of Step 2 in Example 1, except that 4-(4-Isopropoxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**34a**) was used instead of 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**1a**).
MS: 403.3 (M+1 for $C_{24}H_{38}N_2O_3$); an oil; TLC: SiO_2 , R_f 0.50 (3:1 hexanes/
5 EtOAc).

Step 3: (4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**34c**) was prepared in accordance with the methods of Step 3 in Example 1, except that 4-[(4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**34b**) was used instead of 4-[(4-Benzyloxy-phenyl)-(3-
10 methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**1b**).
MS: 303.3 (M+1 for $C_{19}H_{30}N_2O$); an oil; TLC: SiO_2 , R_f 0.24 (8% MeOH/
 CH_2Cl_2).

Step 4: The preparation of Example 26: (4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine was prepared in accordance with
15 the methods of Step 4 in Example 1, except that (4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**34c**) was used instead of (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**1c**).
MS: 373.2 (M+1 for $C_{24}H_{40}N_2O$); an oil; TLC: SiO_2 , R_f 0.5 (10% MeOH/
 CH_2Cl_2);

20 HPLC (C-18 column, 1:1 CH_3CN/H_2O + 0.5% TFA): RT = 3.400 min, 100% pure.

Analysis ($C_{24}H_{40}N_2O \cdot 0.35H_2O$); (calc) C: 76.08, H: 10.83, N: 7.39, (found) C: 76.15, H: 10.84, N: 7.25.

EXAMPLE 35

25 [1-(4-Fluoro-benzyl)-piperidin-4-yl]-(4-isopropoxy-phenyl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 4 in Example 34, except that 4-fluorobenzaldehyde was used instead of isovaleraldehyde.
MS: 411.2 (M+1 for $C_{26}H_{35}N_2O_1F_1$); an oil; TLC: SiO_2 , R_f 0.58 (10% MeOH/
 CH_2Cl_2);

-47-

HPLC (C-18 column, 1:1 CH₃CN/H₂O + 0.5% TFA): RT = 3.488 min, 95% pure.

EXAMPLE 36

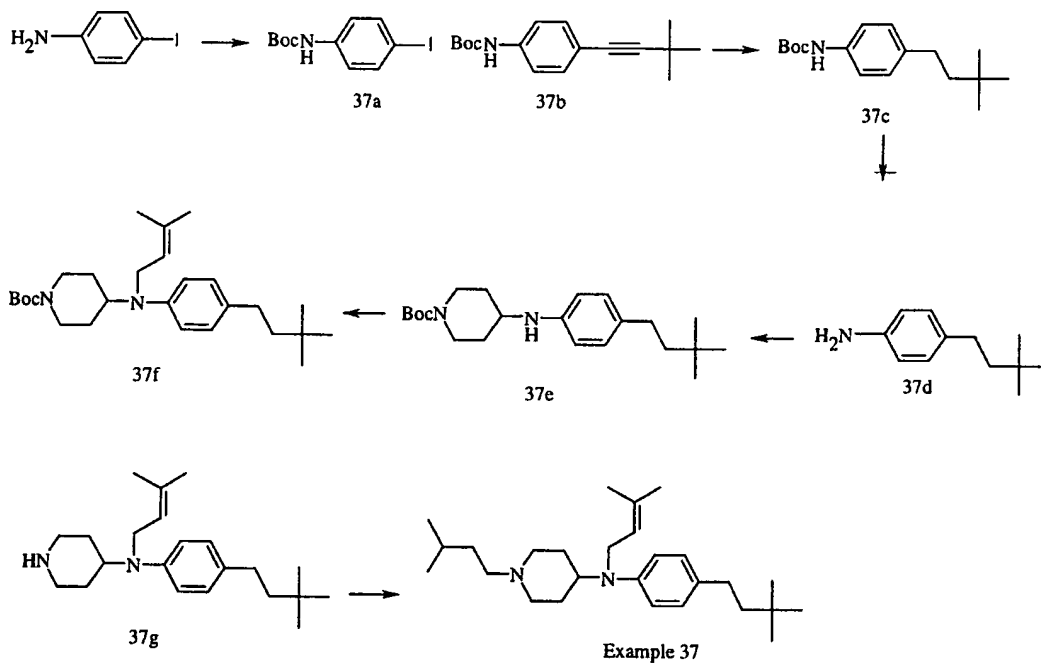
[1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropoxy-phenyl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 4 in Example 34, except that 3,3-dimethylbutylaldehyde was used instead of isovaleraldehyde.

MS: 387 (M+1 for C₂₅H₄₂N₂O); an oil; TLC: SiO₂, R_f 0.2 (2:1 hexanes/EtOAc);

Analysis (C₂₅H₄₂N₂O); (calc) C: 77.67, H: 10.95, N: 7.25, (found) C: 77.34, H:

10.84, N: 7.20.

Scheme VII



EXAMPLE 37

[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine

Step 1: Preparation of (4-Iodo-phenyl)-carbamic acid tert-butyl ester (37a): 4-iodoaniline (10.0 g, 45.6 mmol) was dissolved in THF (50 mL) in an amber flask, cooled to 0°C, and treated with tert-butoxycarbonyl anhydride. The reaction was

-48-

heated to 60°C overnight, then concentrated in vacuo to give 15.5 g (106%) of the crude product which was used without further purification.

MS: 318.0 (M-1 for $C_{11}H_{14}N_1O_2I_1$ in APCI⁻ spectrum); TLC: SiO₂, R_f 0.42 (6:1 hexanes/EtOAc).

5 Step 2: Preparation of [4-(3,3-Dimethyl-but-1-ynyl)-phenyl]-carbamic acid tert-butyl ester (**37b**): (4-Iodo-phenyl)-carbamic acid tert-butyl ester (**37a**, 1.0 g, 3.13 g) was dissolved in THF (30 mL) and treated with Et₃N (2.2 mL, 15.7 mmol), 3,3-dimethyl-1-butyne (0.58 mL, 4.70 mmol), bis(triphenylphosphine) palladium (II) chloride (0.218 g, 0.31 mmol), and copper (I) iodide (0.03 g, 0.16 mmol). The
10 reaction was stirred overnight at room temperature, then filtered and concentrated. The residue was chromatographed on silica gel eluting with 8:1 hexanes/EtOAc to give 0.7 g (82%) of the mostly clean desired product which was carried on without further purification.

15 MS: 272.0 (M-1 for $C_{17}H_{23}N_1O_2$ in APCI⁻ spectrum); TLC: SiO₂, R_f 0.42 (6:1 hexanes/EtOAc).

Step 3: Preparation of [4-(3,3-Dimethyl-butyl)-phenyl]-carbamic acid tert-butyl ester (**37c**): [4-(3,3-Dimethyl-but-1-ynyl)-phenyl]-carbamic acid tert-butyl ester (**37b**, 2.50 g, 9.15 mmol) was treated with 1:1 THF/MeOH (50 mL) and Pd/C (0.5 g, 10%), shaken for 15.8 hours under an atmosphere of H₂ (51.4 psi). More
20 Pd/C (0.5 g, 20%) was added and the reaction was stirred for an additional 1.13 hours, then filtered and concentrated. The crude material was chromatographed on silica gel eluting with 1:9 EtOAc/Hexane to give 2.39 g (94%) of the desired product.

25 MS: 276.2 (M-1 for $C_{17}H_{27}NO_2$ in APCI⁻ spectrum); an oil; TLC: SiO₂, R_f 0.95 (10% MeOH/CH₂Cl₂).

Step 4: Preparation of 4-(3,3-Dimethyl-butyl)-phenylamine (**37d**): [4-(3,3-Dimethyl-butyl)-phenyl]-carbamic acid tert-butyl ester (**37c**, 2.39 g, 8.60 mmol) was dissolved in CH₂Cl₂ (30 mL) and treated with TFA (30 mL) and stirred for 30 minutes. The solution was concentrated down and pumped under high vacuum

-49-

for 10 minutes. The reaction was diluted with EtOAc (500 mL), washed three times with saturated bicarbonate solution and once with brine, dried over Na_2SO_4 , and carried on to Step 5 (assuming 100% yield) without further purification.

5 TLC: SiO_2 , R_f 0.70 (10% MeOH/ CH_2Cl_2).

Step 5: 4-[4-(3,3-Dimethyl-butyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester (**37e**) was prepared in accordance with the methods of Step 1 in Example 1, except that 4-(3,3-Dimethyl-butyl)-phenylamine (**37d**) was used instead of 4-Benzyloxyaniline hydrochloride salt.

10 MS: 361.3 ($M+1$ for $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2$); an oil; TLC: SiO_2 R_f 0.48 (3% MeOH/ CH_2Cl_2).

Step 6: 4-[[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**37f**) was prepared in accordance with the methods of Step 2 in Example 1, except that 4-[4-(3,3-Dimethyl-butyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester (**37e**) was used instead of 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**1a**).

15 MS: 429.4 ($M+1$ for $\text{C}_{27}\text{H}_{44}\text{N}_2\text{O}_2$); an oil; TLC: SiO_2 , R_f 0.23 (9:1 hexane/EtOAc).

20 Step 7: [4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**37g**) was prepared in accordance with the methods of Step 3 in Example 1, except that 4-[[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**37f**) was used instead of 4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**1b**).

25 MS: 329.2 ($M+1$ for $\text{C}_{22}\text{H}_{36}\text{N}_2$); an oil; TLC: SiO_2 , R_f 0.14 (10% MeOH/ CH_2Cl_2).

Step 8: The preparation of Example 37: [4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine was prepared in

-50-

accordance with the methods of Step 4 in Example 1, except that [4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**37g**) was used instead of (4-Benzoyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**1c**).

5 MS: 399.3 (M+1 for $C_{27}H_{46}N_2$); an oil; TLC: SiO_2 , R_f 0.26 (5% MeOH/ CH_2Cl_2);

Analysis ($C_{27}H_{46}N_2$); (calc) C: 81.34, H: 11.63, N: 7.03, (found) C: 81.23, H: 11.49, N: 6.98.

EXAMPLE 38

10 [4-(3,3-Dimethyl-butyl)-phenyl]-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 8 in Example 37, except that 3,3-dimethylbutyraldehyde was used instead of isovaleraldehyde. The final compound was converted to the HCl salt.

MS: 413 (M+1 for $C_{28}H_{48}N_2$); mp 195°C (dec.);

15 HRMS: (calc) 413.3896 (found) 413.3895.

EXAMPLE 39

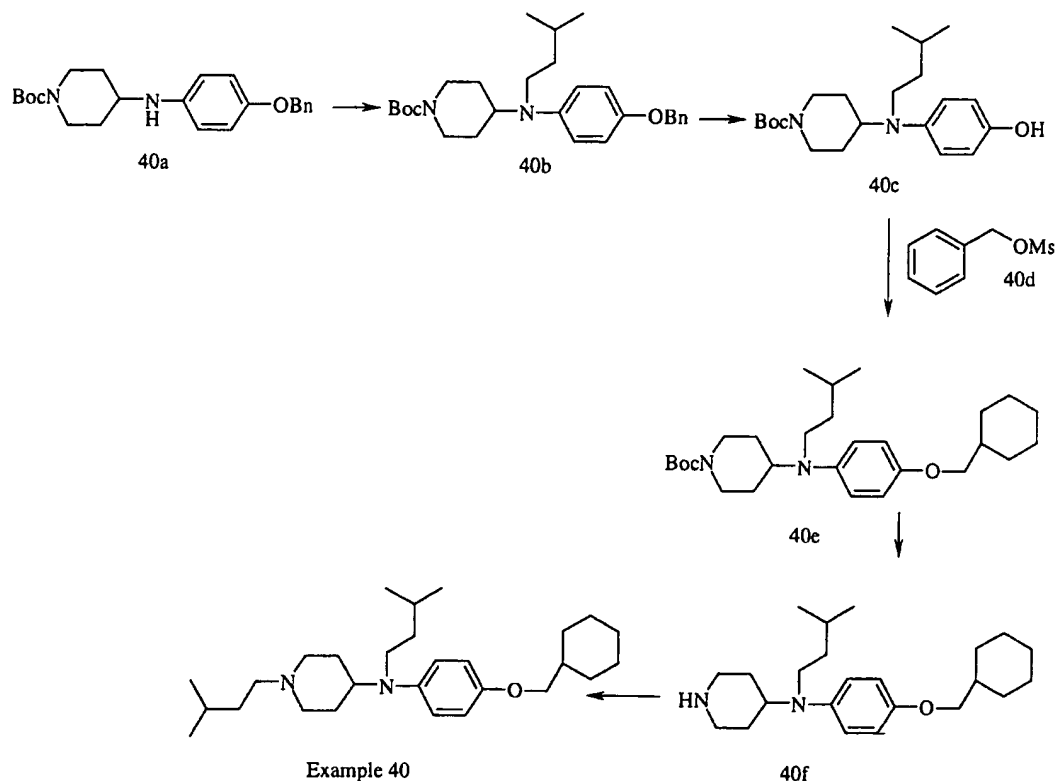
[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-[4-(3,3-dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-amine was prepared in accordance with the methods of Step 8 in Example 37, except that 4-dimethylaminobenzaldehyde was used instead of isovaleraldehyde.

20

MS: 462.4 (M+1 for $C_{31}H_{47}N_3$); an oil; TLC: SiO_2 , R_f 0.27 (6% MeOH/ CH_2Cl_2);

HPLC (C-18 column, 1:1 CH_3CN/H_2O + 0.5% TFA): RT = 3.612 min, 100% pure.

-51-

Scheme VIII**EXAMPLE 40**

(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine

Step 1: 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**40a**) was prepared according to Step 1 in Example 1.

Step 2: Preparation of 4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**40b**): 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**40a**, 3.0 g, 7.84 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with isovaleraldehyde (0.84 mL, 7.84 mmol). The reaction was stirred for 30 minutes, then cooled to 0°C , treated with $\text{NaBH}(\text{OAc})_3$, and stirred overnight. The reaction was diluted with EtOAc (400 mL), washed with saturated bicarbonate solution and brine, dried over

-52-

Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluting with 6% MeOH/CH₂Cl₂ to give 3.3 g (93%) of the desired product.

MS: 453.3 (M+1 for C₂₈H₄₀N₂O₃); an oil; TLC: SiO₂, R_f 0.34 (6% MeOH/CH₂Cl₂);

5 Analysis (C₂₈H₄₀N₂O₃); (calc) C: 74.30, H: 8.91, N: 6.19, (found) C: 74.34, H: 9.08, N: 6.04.

Step 3: Preparation of 4-[(4-Hydroxy-phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**40c**): 4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**40b**, 14.53 g, 32.10 mmol) was treated with 1:1 THF/MeOH (200 mL) and Pd/C (1.5 g, 20%). Shaken for 14 hours under an atmosphere of H₂ (49.7 psi), filtered, and concentrated to give 13.80 g (119%) of the crude product which was used without further purification.

10 MS: 363.2 (M+1 for C₂₁H₃₄N₂O₃); sticky solid; TLC: SiO₂, R_f 0.61 (10% MeOH/CH₂Cl₂);
15 Analysis (C₂₁H₃₄N₂O₃·0.35H₂O); (calc) C: 68.39, H: 9.48, N: 7.60, (found) C: 68.60, H: 9.83, N: 7.33.

Step 4a: Preparation of Methanesulfonic acid cyclohexylmethyl ester (**40d**): Cyclohexylmethanol (1.25 mL, 10.0 mmol) was dissolved in CH₂Cl₂ (50 mL), treated with diisopropylethylamine (7.0 mL, 40.0 mmol), cooled to 0°C, treated with methanesulfonyl chloride (0.85 mL, 11.0 mmol), and stirred for 1 hour at room temperature. The reaction was diluted with CH₂Cl₂ (200 mL), washed with saturated bicarbonate solution and brine, dried over Na₂SO₄, and concentrated to give 2.42 g (125% crude yield) of the desired product which was used immediately without purification.

25 ¹H NMR (CDCl₃) δ 0.91-1.75 (m, 11 H), 2.96 (s, 3 H), 3.98 (d, 2 H, J = 6.3 Hz).

Step 4b: Preparation of 4-[(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**40e**): 4-[(4-Hydroxy-

-53-

phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (40c, 1.01 g, 2.77 mmol) was dissolved in DMF (28 mL), cooled to 0°C, treated with NaH (0.22 g, 60% dispersion in mineral oil, 5.54 mmol), stirred 10 minutes, treated with Methanesulfonic acid cyclohexylmethyl ester (40d, 0.222 g, 5.54 mmol) and heated to 50°C for 2 hours. The reaction was treated further with NaH (0.11 g, 2.77 mmol) and heated to 50°C overnight. The reaction was diluted with EtOAc (200 mL), washed with saturated bicarbonate solution and brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluting with 5:1 hexane/EtOAc to give 1.08 g (85%) of the desired product.

MS: 459.4 (M+1 for C₂₈H₄₆N₂O₃); an oil; TLC: SiO₂, R_f 0.64 (3:1 hexane/EtOAc);

Analysis (C₂₈H₄₆N₂O₃); (calc) C: 73.32, H: 10.11, N: 6.11, (found) C: 73.64, H: 9.80, N: 6.01.

Step 5: Preparation of (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-piperidin-4-yl-amine (40f): 4-[(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (40e, 1.08 g, 2.36 mmol) was dissolved in CH₂Cl₂ (8 mL), treated with TFA (8 mL), and stirred for 30 minutes. The reaction was concentrated in vacuo, diluted with EtOAc (200 mL), washed three times with saturated bicarbonate solution and once with brine, dried over Na₂SO₄, and concentrated to give 0.78 (92%) of the desired product which was used without further purification.

MS: 359.2 (M+1 for C₂₃H₃₈N₂O₁); an oil; TLC: SiO₂, R_f 0.21 (10% MeOH/CH₂Cl₂);

HPLC (C-18 column, 1:1 CH₃CN/H₂O + 0.5% TFA): RT = 5.45 min, 100% pure.

Step 6: The preparation of Example 40: (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine: (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-piperidin-4-yl-amine (40f, 0.20 g, 0.56 mmol) was dissolved in CH₂Cl₂ (4 mL), treated with isovaleraldehyde (61 µL, 0.56 mmol), stirred for 30 minutes, cooled to 0°C, treated with NaBH(OAc)₃ (0.177 g, 0.84

-54-

mmol) and stirred overnight at room temperature. The reaction was diluted with EtOAc (100 mL), washed with saturated bicarbonate solution and brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluting with 4% MeOH/CH₂Cl₂ to give 201 mg (84%) of the desired product.

5 MS: 429.3 (M+1 for C₂₈H₄₈N₂O₁); an oil; TLC: SiO₂, R_f 0.26 (6% MeOH/CH₂Cl₂);

Analysis (C₂₈H₄₆N₂O₃·0.2H₂O); (calc) C: 77.79, H: 11.28, N: 6.48, (found) C: 77.93, H: 11.11, N: 6.31.

EXAMPLE 41

10 4-{4-[(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-butan-2-ol was prepared in accordance with the methods of Step 7 in Example 40, except that 3-hydroxybutyraldehyde was used instead of isovaleraldehyde.

MS: 431.4 (M+1 for C₂₇H₄₆N₂O₂); an oil; TLC: SiO₂, R_f 0.30 (7% MeOH/CH₂Cl₂);

15 Analysis (C₂₇H₄₆N₂O₂); (calc) C: 75.30, H: 10.77, N: 6.50, (found) C: 75.31, H: 10.44, N: 6.33.

EXAMPLE 42

(4-Cyclohexylmethoxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine was prepared in accordance with the methods of Step 7 in
20 Example 40, except that 3,3-dimethylbutyraldehyde was used instead of isovaleraldehyde.

MS: 443 (M+1 for C₂₈H₅₀N₂O₁); sticky solid; TLC: SiO₂, R_f 0.40 (2:1 hexane/EtOAc);

25 Analysis (C₂₈H₅₀N₂O₁); (calc) C: 78.68, H: 11.38, N: 6.33, (found) C: 78.62, H: 11.21, N: 6.24.

EXAMPLE 43

Step 1: Methanesulfonic acid 4-fluoro-benzyl ester (**43a**) was prepared in accordance with the methods of Step 4 in Example 40, except that 4-fluorobenzyl alcohol was used instead of cyclohexylmethanol.

5 MS: 205.2 (M+1 for $C_8H_9F_1O_3S_1$); sticky solid; TLC: SiO_2 , R_f 0.41 (2:1 hexane/EtOAc).

Step 2: 4-[[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**43b**) was prepared in accordance with the methods of Step 5 in Example 40, except that Methanesulfonic acid 4-fluoro-benzyl ester (**43a**) was used instead of Methanesulfonic acid cyclohexylmethyl ester (**40d**).

10 MS: 471.2 (M+1 for $C_{28}H_{39}N_2O_3F_1$); an oil; TLC: SiO_2 , R_f 0.35 (4:1 hexane/EtOAc);
Analysis ($C_{28}H_{39}N_2O_3F_1$); (calc) C: 71.46, H: 8.35, N: 5.95, (found) C: 71.37,
15 H: 8.09, N: 5.73.

Step 3: [4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-piperidin-4-yl-amine (**43c**) was prepared in accordance with the methods of Step 6 in Example 40, except that 4-[[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**43b**) was used instead of 4-[(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**40e**).

20 MS: 371.2 (M+1 for $C_{23}H_{31}N_2O_1F_1$); an oil; TLC: SiO_2 , R_f 0.41 (10% MeOH/ CH_2Cl_2);
Analysis ($C_{23}H_{31}N_2O_1F_1 \cdot 0.8H_2O \cdot 0.5TFA$); (calc) C: 65.23, H: 7.55, N: 6.34,
25 (found) C: 65.25, H: 7.57, N: 6.22.

Step 4: The preparation of Example 43: [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-[4-(4-fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-amine was prepared in accordance with the methods of Step 7 in Example 40, except that [4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-piperidin-4-yl-amine (**43c**) was used instead

-56-

of (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-piperidin-4-yl-amine (**40f**) and 3,3-dimethylbutyraldehyde was used instead of isovaleraldehyde.

MS: 456 (M+1 for $C_{29}H_{43}N_2O_1F_1$); sticky solid; TLC: SiO_2 , R_f 0.35 (1:1 hexanes/EtOAc);

5 Analysis ($C_{29}H_{43}N_2O_1F_1$); (calc) C: 76.61, H: 9.53, N: 6.16, (found) C: 76.78, H: 9.28, N: 6.15.

EXAMPLE 44

(S)-1-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-2-hydroxy-4-methyl-pentan-1-one: (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-
10 piperidin-4-yl-amine (**Ic**) (0.89 g, 2.54 mmol) was dissolved in DMF (17 mL) and treated with N,N-diisopropylethylamine (1.77 mL, 10.17 mmol), L-2-hydroxyisocaproic acid (0.34 g, 2.54 mmol), and HBTU (0.96 g, 2.54 mmol). The reaction was stirred for 3 hours, then diluted with EtOAc (200 mL), washed with saturated bicarbonate solution and brine, dried over Na_2SO_4 , and
15 concentrated. The residue was chromatographed on silica gel eluting with 4% MeOH/ CH_2Cl_2 to give 0.58 g (49%) of the desired product.

MS: 465.2 (M+1 for $C_{29}H_{40}N_2O_3$); an oil; TLC: SiO_2 , R_f 0.47 (5% MeOH/ CH_2Cl_2);

Analysis ($C_{29}H_{40}N_2O_3$); (calc) C: 74.96, H: 8.68, N: 6.03, (found) C: 74.59, H: 8.65, N: 5.87.
20

EXAMPLE 45

(S)-2-Hydroxy-1-{4-[(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-4-methyl-pentan-1-one was made in accordance with the methods of Example 44 except that (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-piperidin-
25 4-yl-amine (**26c**) was used instead of **Ic** (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine.

MS: 401.3 (M+1 for $C_{25}H_{40}N_2O_2$); an oil; TLC: SiO_2 , R_f 0.27 (3:1 hexane/EtOAc);

-57-

Analysis ($C_{25}H_{40}N_2O_2$); (calc) C: 74.96, H: 10.06, N: 6.99, (found) C: 74.77, H: 9.70, N: 6.87.

EXAMPLE 46

The preparation of (3-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-
5 (3-methyl-but-2-enyl)-amine

Step 1: 4-(3-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester
(46a): was prepared in accordance with the methods of Step 1 in Example 1,
except that 3-benzyloxyaniline was used instead of 4-benzyloxyaniline
hydrochloride salt.

10 MS: 383.2 (M+1 for $C_{23}H_{30}N_2O_3$); an oil; TLC: SiO_2 , R_f 0.8 (10%
MeOH/ CH_2Cl_2).

Step 2: 4-[(3-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-
carboxylic acid tert-butyl ester (46b) was prepared in accordance with the
methods of Step 2 in Example 1, except that 4-(3-Benzyloxy-phenylamino)-
15 piperidine-1-carboxylic acid tert-butyl ester (46a) was used instead of 4-(4-
Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (Ia).
MS: 451.3 (M+1 for $C_{28}H_{38}N_2O_3$); an oil; TLC: SiO_2 , R_f 0.37 (10:1 Hexane/
EtOAc).

Step 3: (3-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (46c)
20 was prepared in accordance with the methods of Step 3 in Example 1, except that
4-[(3-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic
acid tert-butyl ester (46b) was used instead of 4-[(4-Benzyloxy-phenyl)-(3-
methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (Ib).
MS: 351.2 (M+1 for $C_{23}H_{30}N_2O$); sticky solid; TLC: SiO_2 , R_f 0.25 (10%
25 MeOH/ CH_2Cl_2).

Step 4: The preparation of Example 46: (3-Benzyloxy-phenyl)-[1-(3,3-dimethyl-
butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine was prepared in accordance
with the methods of Step 4 in Example 1 except that (3-Benzyloxy-phenyl)-(3-

-58-

methyl-but-2-enyl)-piperidin-4-yl-amine (**46c**) was used instead of (4-Benzoyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**1c**).

MS: 435 (M+1 for $C_{29}H_{42}N_2O_1$); sticky solid; TLC: SiO_2 , R_f 0.70 (1:1 hexanes/EtOAc);

5 Analysis ($C_{29}H_{42}N_2O_1$); (calc) C: 80.13, H: 9.74, N: 6.44, (found) C: 79.88, H: 9.04, N: 6.39.

EXAMPLE 47

[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine was prepared in accordance with the methods of
10 Steps 1-8 in Example 37 except that pyrrole-2-carboxaldehyde was used instead of isovaleraldehyde in Step 8. The compound was further prepared as the HCl salt.
MS: 408 (M+1 for $C_{27}H_{41}N_3$); mp 317-319°C.

EXAMPLE 48

[1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-(4-phenethyl-phenyl)-amine
15

Step 1: (4-Iodo-phenyl)-carbamic acid tert-butyl ester (**48a**) was prepared in accordance with the methods of Step 1 in Example 37.

Step 2: (4-Phenylethynyl-phenyl)-carbamic acid tert-butyl ester (**48b**) was prepared in accordance with the methods of Step 2 in Example 37 except that
20 phenylacetylene was used instead of 3,3-dimethyl-1-butyne.

MS: 292.1 (M-1 for $C_{19}H_{19}N_1O_2$ in APCI⁻ spectrum); TLC: SiO_2 , R_f 0.24 (6:1 hexane/EtOAc)

Step 3: (4-Phenethyl-phenyl)-carbamic acid tert-butyl ester (**48c**) was prepared in accordance with the methods of Step 3 in Example 37 except that (4-
25 Phenylethynyl-phenyl)-carbamic acid tert-butyl ester (**48b**) was used instead of [4-(3,3-Dimethyl-but-1-ynyl)-phenyl]-carbamic acid tert-butyl ester (**37b**).

MS: 296.1 (M-1 for $C_{19}H_{23}N_1O_2$ in APCI⁻ spectrum); TLC: SiO_2 , R_f 0.34 (6:1 hexane/EtOAc).

-59-

Step 4: 4-Phenethyl-phenylamine (**48d**) was prepared in accordance with the methods of Step 4 in Example 37 except that (4-Phenethyl-phenyl)-carbamic acid tert-butyl ester (**48c**) was used instead of [4-(3,3-Dimethyl-butyl)-phenyl]-carbamic acid tert-butyl ester (**37c**).

5 MS: 239.2 (M+1 for $C_{14}H_{15}N_1 \cdot CH_3CN$); TLC: SiO_2 , R_f 0.47 (10% MeOH/ CH_2Cl_2).

Step 5: 4-(4-Phenethyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**48e**) was prepared in accordance with the methods of Step 5 in Example 37 except that 4-Phenethyl-phenylamine (**48d**) was used instead of 4-(3,3-Dimethyl-butyl)-phenylamine (**37d**). The mass spectrum of the crude product showed both the expected peak (381.1) and incompletely reduced alkene (379.1). The crude mixture was dissolved in MeOH (75 mL), treated with Raney nickel (1.0 g), and shaken for 1 hour under an atmosphere of H_2 (50 psi). The reaction was filtered, concentrated, and carried on without further purification.

10 MS: 381.1 (M+1 for $C_{24}H_{32}N_2O_2$); TLC: SiO_2 , R_f 0.79 (2:1 hexane/EtOAc).

Step 6: 4-[(3-Methyl-but-2-enyl)-(4-phenethyl-phenyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**48f**) was prepared in accordance with the methods of Step 6 in Example 37 except that 4-(4-Phenethyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**48e**) was used instead of 4-[4-(3,3-Dimethyl-butyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester (**37e**).

20 MS: 449.3 (M+1 for $C_{29}H_{40}N_2O_2$); an oil; TLC: SiO_2 , R_f 0.53 (5:1 hexane/EtOAc);

Analysis ($C_{29}H_{40}N_2O_2$); (calc) C: 77.17, H: 9.00, N: 6.21, (found) C: 77.19, H: 9.00, N: 6.17.

25 Step 7: (3-Methyl-but-2-enyl)-(4-phenethyl-phenyl)-piperidin-4-yl-amine (**48g**) was prepared in accordance with the methods of Step 7 in Example 37 except that 4-[(3-Methyl-but-2-enyl)-(4-phenethyl-phenyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**48f**) was used instead of 4-[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (**37f**).

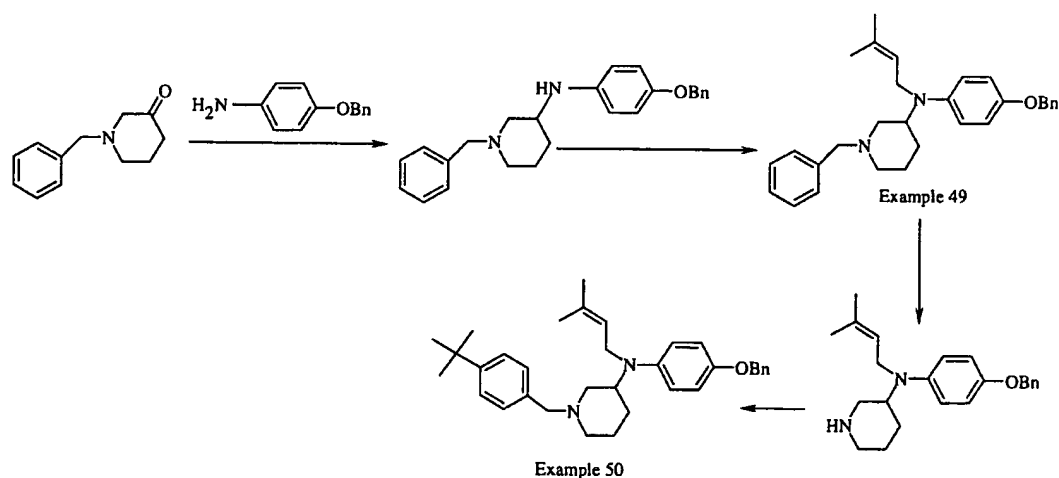
-60-

MS: 349.2 (M+1 for C₂₄H₃₂N₂); an oil; TLC: SiO₂, R_f 0.25 (10% MeOH/CH₂Cl₂).

Step 8: The preparation of Example 48: [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-(4-phenethyl-phenyl)-amine was prepared in accordance with the methods of Step 8 in Example 37 except that (3-Methyl-but-2-enyl)-(4-phenethyl-phenyl)-piperidin-4-yl-amine (**48g**) was used instead of [4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**37g**) and 3,3-dimethylbutyraldehyde was used instead of isovaleraldehyde.

MS: 428 (M+1 for C₃₀H₄₀N₂); an oil; TLC: SiO₂, R_f 0.2 (1:2 hexanes/EtOAc).

Scheme IX



EXAMPLE 49

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-3-yl)-(3-methyl-but-2-enyl)-amine

Step 1: (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-3-yl)-amine (**49a**) was prepared in accordance with the procedures in Example 1 (Step 1) except that 1-benzyl-3-piperidone was used instead of 1-Boc-4-piperidone.

MS: 373 (M+1 for C₂₅H₂₈N₂O₁); TLC: SiO₂ R_f 0.6 (5% MeOH/CH₂Cl₂);

Analysis (C₂₅H₂₈N₂O₁): (Cal.) C: 79.84, H: 7.61, N: 7.45, (found) C: 79.83, H: 7.56, N: 7.45.

-61-

Step 2: The preparation of Example 49: (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-3-yl)-(3-methyl-but-2-enyl)-amine was prepared in accordance with the procedure in Example 1 (Step 2) except that (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-3-yl)-amine (**49a**) was used instead of 4-(4-Benzyloxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (**Ia**).

MS: 441 (M+1 for $C_{30}H_{36}N_2O_1$); oil; TLC: SiO_2 R_f = 0.5 (66% hexanes/EtOAc);

Analysis ($C_{30}H_{36}N_2O_1$): (Cal.) C: 81.78, H: 8.24, N: 6.36, (found) C: 81.81, H: 8.26, N: 6.31.

EXAMPLE 50

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine

Step 1: The preparation of (4-Benzyloxy-phenyl)-(1-piperidin-3-yl)-(3-methyl-but-2-enyl)-amine (**50a**): (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-3-yl)-(3-methyl-but-2-enyl)-amine (**49b**) (0.90 g, 2.04 mmol) was dissolved in 1,2-dichloroethane (20 mL), cooled to 0°C, and treated with α -chloroethylchloroformate (0.24 mL, 2.04 mmol). The reaction was stirred cold for 15 minutes, then heated to 60°C for 1 hour. The reaction was cooled to room temperature, concentrated in vacuo, re-dissolved in MeOH (20 mL), heated to 50°C for 1 hour, then concentrated in vacuo to give 0.86 g (>100%) of the crude material which was carried on without further purification.

MS: 351 (M+1 for $C_{23}H_{30}N_2O$); oil; TLC: SiO_2 R_f = 0.1 (10% MeOH/ CH_2Cl_2).

Step 2: The preparation of Example 50: (4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine was prepared in accordance with methods of Example 3 except that (4-Benzyloxy-phenyl)-(1-piperidin-3-yl)-(3-methyl-but-2-enyl)-amine (**50a**) was used instead of (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-piperidin-4-yl-amine (**Ic**).

-62-

MS: 497.3 (M+1 for $C_{34}H_{44}N_2O_1$); an oil; TLC: SiO_2 R_f = 0.37 (5% MeOH/ CH_2Cl_2);

HPLC (C-18 column, 1:1 CH_3CN/H_2O + 0.5% TFA): RT = 15.162 min, 93% pure.

5

BIOLOGICAL ACTIVITY

The compounds of the present invention exhibit valuable biological properties because of their ability to block calcium flux through N-type voltage-gated calcium channels. To measure interaction at the N-type Ca^{2+} channel and calcium flux inhibition, the effects of the compounds of the present invention were measured in the assays described below.

10

Measurement of N-type Ca^{2+} Channel Blocking Potencies of Compounds in IMR-32 Cells Using the Fluorescent Ca^{2+} Indicator Indo-1

IMR-32 cells are a human tumor cell line of neural origin. The IMR-32 cell line has been shown to contain both N- and L-type voltage sensitive calcium channels. Calcium flux into these cells may be induced by stimulation with elevated potassium concentrations. The L-channel component of calcium flux may be blocked by adding 5 μM nitrendipine. The remaining component of calcium entry into the IMR-32 cells is due to calcium flux through N-type calcium channels. Intracellular calcium concentrations are measured using the fluorescent calcium indicator Indo-1. The effect of drug concentration on calcium uptake is studied.

15

20

Methods

The IMR-32 cell line was obtained from the American Type Culture Collection (Rockville, MD). Cells were grown in Eagle's Minimum Essential Medium with Earle's salts supplemented with 10% fetal bovine serum, 2 mM L-Gln and antibiotic/antimycotic mixture (Gibco). At approximately 80% confluency, differentiation was induced by the addition of 1 mM dibutyryl cAMP and 2.5 μM bromodeoxyuridine to the medium. After seven to thirteen days of

25

-63-

differentiation, cells were detached using 0.5 mM EDTA and loaded with five 1M Indo-1 acetoxymethyl ester (Molecular Probes, Eugene, OR) at 30°C for forty-five minutes. Loaded cells were washed twice, resuspended ($\sim 10^7$ cells/mL) in assay buffer (10 mM HEPES/Tris pH 7.4 in Hank's Balanced Salt Solution without bicarbonate or phenol red containing 0.5% bovine serum albumin) and kept on ice until use. Fluorescence measurements were carried out in a Photon Technology International (PTI, South Brunswick, NJ) Model RF-F3004 spectrofluorometer with dual emission monochromators using excitation at 350 nm and emission at 400 and 490 nm. The instrument was equipped with a thermostated cuvette holder with stirring capabilities as well as with a computer-controlled pump which allowed for reagent addition during measurement. Instrument control and data collection was done by PTI's OSCAR software running on an IBM compatible computer. Different concentrations of the test compounds (60 μ L in dimethyl sulfoxide) were added to 5.94 mL of assay buffer containing approximately 3×10^6 loaded cells, and 5 μ M Nitrendipine (in 30 μ L EtOH) to block L-type Ca^{2+} channels. Samples were incubated for ten minutes at 30°C and then aliquoted into three 10 \times 10 mm disposable acrylic cuvettes. Emission signals at 400 and 490 nm were acquired from each cuvette at 30°C for fifty seconds. At twenty seconds after the start of reading, cells were depolarized by the addition of 160 μ L of stimulation solution (1M KCl, 68 mM CaCl_2) to the cuvette via the computer-controlled pump. Ratio of dual emission signals (400 nm/490 nm), which is proportional to intracellular Ca^{2+} concentration, was plotted against time, and the difference between maximal response after stimulation and basal value (before stimulation) was determined. Values obtained in this way were plotted as a function of drug concentration. IC_{50} values of test compounds were calculated by fitting a four-parameter logistic function to the data using the least squares method.

In Vivo Biological Protocol:

A compound of the present invention was dissolved in water using 10% (weight/volume) Emulphor (GAF Corp., Wayne, NJ) surfactant. Substances were administered by intravenous injection into the retro-orbital venous sinus. All

testing was performed fifteen minutes or forty-five minutes after drug injection. All the male mice, 3-4 weeks old were obtained from Jackson Laboratories Bar Harbour, ME. Immediately before anticonvulsant testing, mice were placed upon a wire mesh, four inches square suspended from a steel rod. The square was slowly inverted through 180 degree and mice observed for thirty seconds. Any mouse falling from the wire mesh was scored as ataxia.

Mice were placed into an enclosed acrylic plastic chamber (21 cm height, approximately 30 cm diameter) with a high-frequency speaker (4 cm diameter) in the center of the top lid. An audio signal generator (Protek model B-810) was used to produce a continuous sinusoidal tone that was swept linearly in frequency between 8 kHz and 16 kHz once each 10 msec. The average sound pressure level (SPL) during stimulation was approximately 100 dB at the floor of the chamber. Mice were placed within the chamber and allowed to acclimatize for one minute. DBA/2 mice in the vehicle-treated group responded to the sound stimulus (applied until tonic extension occurred, or for a maximum of sixty seconds) with a characteristic seizure sequence consisting of wild running followed by clonic seizures, and later by tonic extension, and finally by respiratory arrest and death in 80% or more of the mice. In vehicle-treated mice, the entire sequence of seizures to respiratory arrest lasts approximately 15-20 seconds.

The incidence of all the seizure phases in the drug-treated and vehicle-treated mice was recorded, and the occurrence of tonic seizures were used for calculating anticonvulsant ED₅₀ values by probit analysis. Mice were used only once for testing at each time and dose point. Results of this assay are shown below in Table 2.

Anti-Writhing Test in Mice (AW) Test Protocol

The purpose of this test is to evaluate drugs for analgesic-like activity. The AW test determines the effect of drugs on the response to a presumed painful stimulus in mice and is used as a preliminary *in vivo* procedure for the identification of potential analgesic agents.

Known analgesics with low, moderate, or high efficacy in man allow mice to tolerate intra-peritoneal administration of dilute acetic acid as evidenced by lesser incidence of writhing movements. The AW test measures the nociceptive

-65-

response to acetic acid in mice and provides an objective, reliable, and quantitative estimate of efficacy and potency of potential analgesic compounds. This test serves as a preclinical predictor of analgesic activity.

Subjects are male Swiss-Webster mice (25-35 g).

5 Compounds are dissolved or suspended in physiological saline containing 2% Emulphor. Suspensions are subjected to ultrasonication for 3 minutes. Drug doses are expressed as the active moiety and are normally administered to mice (10, 30, and 100 mg/kg IP, SC, PO, or IM) in a volume of 10 mL/kg, 1 hour prior to testing; ICV doses (in μ g/kg) are administered in a volume of 0.5 mL/kg, 10 5 minutes prior to testing. Animals dosed PO are fasted for 16 hours prior to dosing. Groups of eight mice are tested with each dose or the vehicle solution (control group).

 Mice are treated with a dilute solution of acetic acid (0.6%, 10 mL/kg IP) which elicits writhing. In four successive trials, one pair of mice from each 15 treatment group is placed in one of four adjacent clear plexiglas chambers (4 in \times 4 in \times 4 in). This allows the simultaneous observation of four pairs of mice representing all treatments and controls throughout the test. Writhing movements (abdominal contractions, stretching of the torso and hind legs, and concave arching of the back) are counted for 5 minutes commencing 7 minutes after acetic 20 acid administration.

 Drug effects on acetic acid-induced writhing are expressed as percent suppression of writhing relative to the vehicle-treated control group run in parallel with treated animals. The writhing tallies from pairs of animals are summed for each treatment and are divided by the summed writhing in the control group. The 25 ED₅₀s for suppression of writhing are determined by nonlinear regression analysis. Each dose is assigned a rating as follows:

N = not active: 0-30% inhibition of writhing

C = moderately active: 31-60% inhibition

A = active: 61-100% inhibition

TABLE 1. In Vitro Results

Example Number	IMR 32	
	% of Blockade	
	@ μM	
1	79% @ 10, 40% @ 1	
2	93% @ 10, 62% @ 1	
3	96% @ 1	
4	94% @ 10, 63% @ 1	
5	100% @ 10, 47% @ 1	
6	$\text{IC}_{50} = 0.33$	
7	$\text{IC}_{50} = 0.58$	
8	71% @ 10, 16% @ 1	
9	100% @ 10, 30% @ 1	
10	62% @ 10, 15% @ 1	
11	80% @ 10, 41% @ 1	
12	75% @ 10, 49% @ 1	
13	75% @ 10, 37% @ 1	
14	88% @ 10, 44% @ 1	
15	92% @ 10, 51% @ 1	
16	78% @ 10, 45% @ 1	
17	76% @ 10, 86% @ 1	
18	$\text{IC}_{50} = 0.92$, 88% @ 10, 60% @ 1	
19	$\text{IC}_{50} = 0.72 \mu\text{M}$	
20	$\text{IC}_{50} = 3.0 \mu\text{M}$	
21	$\text{IC}_{50} = 3.9 \mu\text{M}$	
22	$\text{IC}_{50} = 0.50 \mu\text{M}$	
23	$\text{IC}_{50} = 0.30 \mu\text{M}$	
24	$\text{IC}_{50} = 1.8 \mu\text{M}$	
25	62% @ 1 μM	
26	43% @ 1 μM	
27	15% @ 1 μM	
28	41% @ 1 μM	
29	84% @ 10 μM , 17% @ 1 μM	
30	79% @ 10 μM , 18% @ 1 μM	
31	62% @ 10 μM , 7% @ 1 μM	
32	70% @ 10 μM , 0% @ 1 μM	

TABLE 1. In Vitro Results (cont'd)

Example	IMR 32
Number	% of Blockade @ μM
33	98% @ 10 μM , 54% @ 1 μM
34	76% @ 10 μM , 23% @ 1 μM
35	37% @ 1 μM
36	74% @ 10 μM , 26% @ 1 μM
37	92% @ 10 μM , 31% @ 1 μM
38	83% @ 10 μM , 38% @ 1 μM
39	85% @ 1 μM , 60% @ 1 μM
40	72% @ 1 μM
41	$\text{IC}_{50} = 1.5 \mu\text{M}$
42	81% @ 10 μM , 60% @ 1 μM
43	99% @ 10 μM , 65% @ 1 μM
44	107% @ 10 μM , 64% @ 1 μM
45	85% @ 10 μM , 28% @ 1 μM
46	98% @ 10 μM , 55% @ 1 μM
47	$\text{IC}_{50} = 0.9 \mu\text{M}$
49	$\text{IC}_{50} = 1.2 \mu\text{M}$
50	96% @ 10 μM , 86% @ 1 μM

-68-

TABLE 2. In Vivo Results

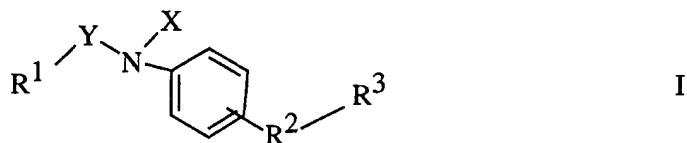
Example	DBA/2 mice % Protection (dose)	Anti-Writhing % Protection (dose)
1	100% @ 30 mg/kg	
2	80% @ 10 mg/kg	49% (10 mg/kg)
5	80% @ 10 mg/kg	
6	100% @ 30 mg/kg	
	100 % @ 10 mg/kg	
7	100% @ 30 mg/kg	
	100 % @ 10 mg/kg	
8	60% (10 mg/kg)	
15	100% @ 30 mg/kg (45 min)	
	20 % @ 10 mg/kg	
19	80% (10 mg/kg)	32% (10 mg/kg)
20	40% (10 mg/kg)	
26		11% (10 mg/kg)
39		95% (10 mg/kg)
42		6.5% (10 mg/kg)
44	100% (30 mg/kg)	100% (30 mg/kg)
		30% (10 mg/kg)

-69-

CLAIMS

What is claimed is:

1. Compounds having the Formula I

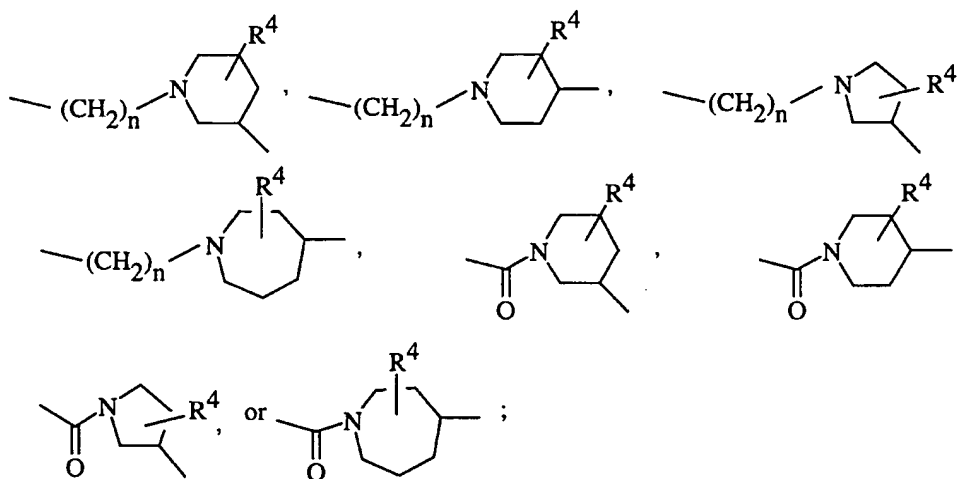


5 wherein

each n is independently 0 to 3;

R^1 is C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, substituted C_3 - C_8 cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_2 - C_8 alkenyl, C_3 - C_8 cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or arylalkyl;

Y is



X is C_1 - C_8 alkyl, C_1 - C_8 substituted alkyl, C_2 - C_8 alkenyl, C_2 - C_8 substituted alkenyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl;

R^2 is absent, -O-, $(CH_2)_n$ -, $O(CH_2)_n$ -, $(CH_2)_nO$ -, $N(R^5)(CH_2)_n$ -, $(CH_2)_nN(R^5)$ -, $S(CH_2)_n$ -, $(CH_2)_nS$ -, -C=C-, or -C≡C-;

-70-

R^3 is monocyclic aryl, substituted monocyclic aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, substituted C_3 - C_{10} cycloalkyl;

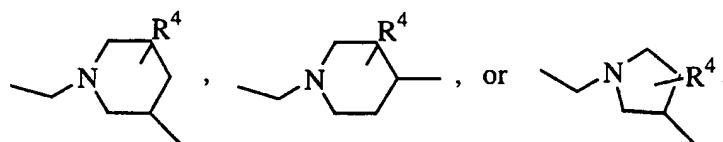
5

R^4 , R^5 are independently H or C_1 - C_8 alkyl; and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

2. A compound in accordance with Claim 1 wherein R^2 is $O(CH_2)_n$ - or $-(CH_2)_n$ - and R^3 is phenyl.

10

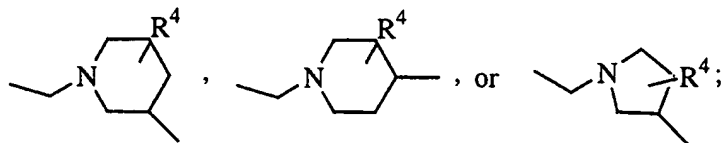
3. A compound in accordance with Claim 1 wherein X is C_2 - C_8 alkenyl or C_1 - C_8 alkyl and Y is



4. A compound in accordance with Claim 1 wherein R^4 is hydrogen and R^1 is 3,3-dimethylbutyl.

15

5. A compound in accordance with Claim 1 wherein R^3 is phenyl; Y is



R^4 is hydrogen;

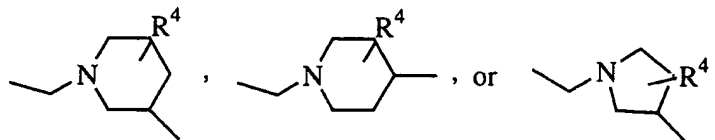
20

X is 3-methyl-but-2 enyl; and

-71-

R^1 is C_1 - C_8 alkyl, substituted C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, substituted C_3 - C_8 cycloalkyl, heterocycloalkyl, substituted heteroalkyl, C_2 - C_8 alkenyl, C_3 - C_8 cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or arylalkyl.

- 5 6. A compound in accordance with Claim 1 wherein Y is



7. A compound in accordance with claim 1 wherein X is 3-methyl-but-2 enyl or 3-methylbutyl.

8. A compound in accordance with claim 1 wherein R^1 is C_1 - C_8 alkyl,
10 phenyl, pyrrolyl, piperazinyl, imidazolyl, pyridyl, or pyranlyl.

9. A compound in accordance with claim 1 wherein R^4 is hydrogen.

10. The compounds:

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

- 15 (4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

- 20 (4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

4-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-ylmethyl}-phenol;

(4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

-72-

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(1H-imidazol-4-ylmethyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

5 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pyridin-2-ylmethyl-piperidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-amine;

10 {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-2-yl]-methanone;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-3-yl]-methanone;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[1-(3-methyl-butyl)-piperidin-4-yl]-methanone;

15 {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

20 {4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[6-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone; or

{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[3-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone.

25 11. The compounds:

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

30 (4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

-73-

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

5 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-4-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

10 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine; or

(4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine.

15 12. The compounds:

(4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

20 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-3-yl]-amine;

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-3-yl]-amine;

25 (4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

30 (4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine; or

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine.

5 13. The compounds:

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-3-yl]-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-3-yl]-amine;

10 (4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

15 (4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-methoxy-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

20 (4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-pyrrolidin-3-yl]-amine; or

25 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-[1-(4-methylsulfanyl-benzyl)-pyrrolidin-3-yl]-amine.

14. The compounds:

(4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

30 (4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-pyrrolidin-3-yl]-(3-methyl-butyl)-amine;

-75-

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-4-yl)-(4-benzyloxy-phenyl)-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

5 (4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-3-yl)-(4-benzyloxy-phenyl)-(3-methyl-butyl)-amine;

10 (4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-3-yl)-(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amine; or

15 (4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine.

15. The compounds:

(4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

20 (1-Benzo[1,3]dioxol-5-ylmethyl-pyrrolidin-3-yl)-(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-bromo-benzyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

25 (4-Benzyloxy-phenyl)-[1-(4-chloro-benzyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

N-Benzyl-N'-[1-(4-tert-butyl-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

N-Benzyl-N'-[1-(4-dimethylamino-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

30 N-Benzyl-N'-[1-(3,3-dimethyl-butyl)]-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

-76-

N-Benzyl-N'-[1-(4-bromo-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine;

N-Benzyl-N'-[1-(4-methoxy-benzyl)-piperidin-4-yl]-N'-(3-methyl-but-2-enyl)-benzene-1,4-diamine; or

5 [1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-(4-phenethyl-phenyl)-amine.

16. The compounds:

(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-4-yl)-(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amine;

10 (4-Benzyloxy-phenyl)-[1-(4-methanesulfinyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-isopropoxy-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

15 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(4-methylsulfanyl-benzyl)-piperidin-4-yl]-amine;

(4-Benzyloxy-phenyl)-[1-(4-ethoxy-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

20 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pentyl-piperidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

25 (4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine; or

(4-Benzyloxy-phenyl)-(3-methyl-butyl)-(1-pentyl-piperidin-4-yl)-amine.

17. The compounds:

30 {4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

-77-

{4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

{4-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;

5 (4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-3-yl]-(3-methyl-butyl)-amine;

10 (4-Benzyloxy-phenyl)-(3-methyl-butyl)-(1-pentyl-piperidin-3-yl)-amine;

{3-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

{3-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

15 {3-[(4-Benzyloxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone; or

(4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine.

18. The compounds:

20 (4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pentyl-piperidin-3-yl)-amine;

25 {3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

{3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

{3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone;

30 (4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

-78-

(4-Benzyloxy-phenyl)-[1-(3-methoxy-3-methyl-butyl)-pyrrolidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-pentyl-pyrrolidin-3-yl)-amine;

5 {3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-pyrrolidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone;

 {3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-pyrrolidin-1-yl}-[4-isopropyl-1-(3-methyl-butyl)-piperazin-2-yl]-methanone; or

10 {3-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-pyrrolidin-1-yl}-[4-methyl-1-(3-methyl-butyl)-piperidin-2-yl]-methanone.

19. The compounds:

 (4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-(3-methyl-but-2-enyl)-amine;

15 4-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-butan-2-ol;

 (4-Benzyloxy-phenyl)-(1-furan-2-ylmethyl-piperidin-4-yl)-(3-methyl-but-2-enyl)-amine;

 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-phenyl-propyl)-piperidin-4-yl]-amine;

20 (4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-phenethyl-piperidin-4-yl)-amine;

 (4-Benzyloxy-phenyl)-[1-(4-methanesulfonyl-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

25 (4-Benzyloxy-phenyl)-[1-(4-fluoro-benzyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

 [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

30 4-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-butan-2-ol; or

 (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine.

20. The compounds:

[1-(4-Fluoro-benzyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

5 (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-(1-pyridin-3-ylmethyl-piperidin-4-yl)-amine;

[1-(1H-Imidazol-4-ylmethyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

2-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-propan-1-ol;

10 (4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

(4-Isopropoxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

15 [1-(4-Fluoro-benzyl)-piperidin-4-yl]-(4-isopropoxy-phenyl)-(3-methyl-but-2-enyl)-amine;

1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(4-isopropoxy-phenyl)-(3-methyl-but-2-enyl)amine;

[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine; or

20 4-(3,3-Dimethyl-butyl)-phenyl]-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine.

21. The compounds:

[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-[4-(3,3-dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-amine;

25 (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(3-methyl-butyl)-piperidin-4-yl]-amine;

4-{4-[(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-amino]-piperidin-1-yl}-butan-2-ol;

30 (4-Cyclohexylmethoxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

[1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-[4-(4-fluoro-benzoyloxy)-phenyl]-(3-methyl-butyl)-amine;

-80-

(S)-1-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-2-hydroxy-4-methyl-pentan-1-one;

(S)-2-Hydroxy-1-{4-[(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-4-methyl-pentan-1-one;

5 (3-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

[4-(3,3-Dimethyl-butyl)-phenyl]-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine; or

10 [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-(4-phenethyl-phenyl)-amine.

22. The compounds:

(4-Benzyloxy-phenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

15 (4-Benzyloxyphenyl)-[1-(4-tert-butyl-benzyl)-piperidin-3-yl]-(3-methyl-but-2-enyl)-amine;

(1-Cyclohexylmethyl-piperidin-4-yl)-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-amine;

20 (1-Cyclohexyl-piperidin-4-yl)-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine;

25 (4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine;

(1-Furan-3-ylmethyl-piperidin-4-yl)-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-(1-thiophen-3-ylmethyl-piperidin-4-yl)-amine; or

30 [1-(3,3-Dimethyl-butyl)-piperidin-4-yl]-[4-(furan-3-ylmethoxy)-phenyl]-(3-methyl-butyl)-amine.

23. The compounds:

[1-(4-Fluoro-benzyl)-piperidin-4-yl]-[4-(furan-3-ylmethoxy)-phenyl]-(3-methyl-butyl)-amine;

[4-(Furan-3-ylmethoxy)-phenyl]-(3-methyl-butyl)-[1-(1H-pyrrol-2-ylmethyl)-piperidin-4-yl]-amine;

[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-(4-isopropyl-phenyl)-(3-methyl-but-2-enyl)-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-[1-(4-fluoro-benzyl)-piperidin-4-yl]-(3-methyl-butyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-(1-phenyl-piperidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-[1-(4-fluoro-phenyl)-piperidin-4-yl]-(3-methyl-but-2-enyl)-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(4-trifluoromethyl-phenyl)-piperidin-4-yl]-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-(1-pyridin-2-ylmethyl-piperidin-4-yl)-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-(1-pyridin-4-ylmethyl-piperidin-4-yl)-amine; or

4-{4-[(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-ylmethyl}-phenol.

24. The compounds:

(4-Isopropyl-phenyl)-(3-methyl-but-2-enyl)-[1-(3,3,3-trifluoropropyl)-piperidin-4-yl]-amine;

(4-Cyclohexylmethoxy-phenyl)-(3-methyl-butyl)-[1-(1H-pyrrol-3-ylmethyl)-piperidin-4-yl]-amine;

[4-(4-Fluoro-benzyloxy)-phenyl]-(3-methyl-butyl)-[1-(1H-pyrrol-3-ylmethyl)-piperidin-4-yl]-amine;

(trans)-2-{4-[(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-cyclohexanol;

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-(3-methyl-butyl)-amine;

-82-

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-cyclohexylmethyl-amine;

(4-Benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-ethyl-amine;

Benzyl-(4-benzyloxy-phenyl)-(1-benzyl-piperidin-4-yl)-amine;

5 (4-Benzyloxy-phenyl)-[1-(4-dimethylamino-benzyl)-piperidin-3-yl]-(3-methyl-butyl)-amine; or

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(1H-pyrrol-3-ylmethyl)-piperidin-3-yl]-amine.

25. The compounds:

10 (1-Benzyl-piperidin-4-yl)-(3-methyl-butyl)-[4-(pyridin-3-ylmethoxy)-phenyl]-amine;

(4-Benzyloxy-phenyl)-(3-methyl-but-2-enyl)-[1-(3,3,3-trifluoropropyl)-piperidin-4-yl]-amine; or

15 (4-Benzyloxy-phenyl)-[1-(3,3-dimethyl-butyl)-piperidin-4-yl]-(3-methyl-butyl)-amine.

26. A pharmaceutical composition comprising a compound of Claim 1.

27. A method of blocking calcium channels, the method comprising administering to a patient in need of calcium channel blocking, a therapeutically effective amount of a compound of Claim 1 to block
20 calcium channels.

28. The method of Claim 27 wherein the calcium channels are N-type calcium channels.

29. A method of blocking N-type calcium channels, the method comprising administering to a patient in need of N-type calcium channel blocking, a therapeutically effective amount of a compound of Claim 1 to block
25 N-type calcium channels.

-83-

30. A method of treating stroke, the method comprising administering to a patient having or having had a stroke a therapeutically effective amount of a compound of Claim 1.
- 5 31. A method of preventing a stroke, the method comprising administering to a patient at risk of having a stroke a therapeutically effective amount of a compound of Claim 1.
32. A method of treating cerebral ischemia, the method comprising administering to a patient having cerebral ischemia a therapeutically effective amount of a compound of Claim 1.
- 10 33. A method of treating head trauma, the method comprising administering to a patient having head trauma a therapeutically effective amount of a compound of Claim 1.
- 15 34. A method of treating pain, the method comprising administering to a patient having pain a therapeutically effective amount of a compound of Claim 1.
35. A method of treating epilepsy, the method comprising administering to a patient having epilepsy a therapeutically effective amount of a compound of Claim 1.
- 20 36. A method of treating asthma, the method comprising administering to a patient having asthma a therapeutically effective amount of a compound of Claim 1.
37. A method of treating amyotrophic lateral sclerosis, the method comprising administering to a patient having amyotrophic lateral sclerosis a therapeutically effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/25007

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/58 A61K31/445 C07D211/56 C07D211/60 C07D211/62
C07D401/06 C07D405/04 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01425 A (SCHERING CORP) 15 January 1998 see page 34 - page 35; claim 1 see page 16; example 10 see pages 23-24; example 5, the compounds no. 28 and 5A-5C see page 26; example 9 see page 29; examples 11C, 11D see page 11, line 4 - line 7 ---	1-3, 5-7, 9, 26
X	WO 93 15052 A (SMITHKLINE BEECHAM PLC) 5 August 1993 see page 40 - page 41; claims 1, 2 see page 1, line 15 - line 16 --- -/-	1-4, 6-9, 26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 March 1999

Date of mailing of the international search report

16. 04. 99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 98/25007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 24390 A (SMITHKLINE BEECHAM PLC ;BROWN THOMAS HENRY (GB); COOPER DAVID GWYN) 14 September 1995 see page 24; claim 1 see page 1, line 14 - line 15 ---	1-3,6,7, 9,26
X	WO 93 25528 A (RICHTER GEDEON VEGYESZET ;DOMANY GYÖRGY (HU); BARTANE SZALAI GIZE) 23 December 1993 see page 30; claim 1 see page 24, line 31 see page 1, line 28 - page 2, line 3 ---	1,3,6,9, 26
X	WO 94 27967 A (SMITHKLINE BEECHAM LAB ;NADLER GUY MARGUERITE MARIE GE (FR); MORVA) 8 December 1994 see page 24; claim 1 see page 1, line 25 - line 32 ---	1,3,6,9, 26
X	US 3 691 176 A (HALLAS ROBERT ET AL) 12 September 1972 see column 1, line 5 - line 22 ---	1,3,6,9, 26
X	US 3 686 187 A (COLE JOHN WAYNE ET AL) 22 August 1972 see column 1, line 24 - line 38 see column 4; example 6 ---	1,3,6,9, 26
X	EP 0 156 433 A (JANSSEN PHARMACEUTICA NV) 2 October 1985 see page 67 - page 68; claim 1 see page 35; compound no. 66 see page 1, line 19 - line 21 ---	1-3,6,7, 9,26
X	WO 97 26258 A (JANSSEN PHARMACEUTICA NV ;STOKBROEKX RAYMOND ANTOINE (BE); AA MARC) 24 July 1997 see page 33 - page 34; claim 1 see page 23; compound no. 142 see page 1, line 4 - line 6 ---	1-3,6,7, 9,26
X	WO 96 18628 A (UPJOHN CO ;ROMERO DONNA L (US); THOMAS RICHARD C (US); MAY PAUL D) 20 June 1996 see page 161 - page 184; claim 1 see page 1, line 6 - line 7 ---	1-3,6-9, 26
A	WO 97 10212 A (NEUROSEARCH AS ;AXELSSON OSKAR (SE); PETERS DAN (SE); OESTERGAARD) 20 March 1997 see page 28 - page 29; claim 1 see page 1, last paragraph -----	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25007

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27-37 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-4, 6, 8, 9, 26-37
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-4,6,8,9,26-37

The novelty search on the compounds of the present claim 1 revealed such a vast amount of novelty-destroying documents that the search and the search report - as far as the question of novelty is concerned - had to be limited to the compounds of the present claim 1 wherein X is 3-methyl-but-2-enyl, 3-methylbutyl, cyclohexylmethyl, ethyl, and benzyl (it appears from the description (cf. all the present examples) that the said X- groups represent an essential structural feature of the present compounds). That is to say, that the present international search report can be considered as being complete with respect to the compounds of the present claims 5, 7, and 10-25.

It is furthermore noted that the term "prodrug" as used in the present claims is vague and unclear (Article 6 PCT) and - as it has no concrete structural meaning - creates a doubt as to the real scope of the present compound claims. Accordingly, the present search and the present search report also had to be limited to those compounds of the present application which are clearly defined by their structural features (as given in the present claims 1-25). The search report cannot therefore be considered as being complete either as far as the "prodrugs" of the present compounds are concerned.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 98/25007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9801425 A	15-01-1998	AU 3581097 A	02-02-1998
WO 9315052 A	05-08-1993	AU 3364493 A	01-09-1993
		EP 0629190 A	21-12-1994
		JP 7503461 T	13-04-1995
WO 9524390 A	14-09-1995	NONE	
WO 9325528 A	23-12-1993	AU 4352193 A	04-01-1994
		CN 1080918 A	19-01-1994
		ZA 9303355 A	17-11-1993
WO 9427967 A	08-12-1994	FR 2705674 A	02-12-1994
		FR 2708607 A	10-02-1995
		AU 6971794 A	20-12-1994
		EP 0700385 A	13-03-1996
		JP 9501404 T	10-02-1997
		ZA 9403594 A	20-04-1995
US 3691176 A	12-09-1972	NONE	
US 3686187 A	22-08-1972	NONE	
EP 0156433 A	02-10-1985	US 5001125 A	19-03-1991
		AT 61050 T	15-03-1991
		AU 576563 B	01-09-1988
		AU 4034885 A	03-10-1985
		BG 43690 A	15-07-1988
		CA 1238321 A	21-06-1988
		CS 8501952 A	18-11-1992
		DK 134185 A,B,	27-09-1985
		FI 851177 A,B,	27-09-1985
		GR 850714 A	14-06-1985
		JP 60226862 A	12-11-1985
		NN 5485 A	22-10-1986
		PT 80157 B	20-03-1987
		SU 1384198 A	23-03-1988
		US 5157035 A	20-10-1991
		US 5292738 A	08-03-1994
		ZM 1785 A	27-03-1986
WO 9726258 A	24-07-1997	AU 1443997 A	11-08-1997
		CA 2237273 A	24-07-1997
		EP 0876366 A	11-11-1998
		NO 982037 A	15-09-1998
WO 9618628 A	20-06-1996	AU 4151696 A	03-07-1996
		EP 0797576 A	01-10-1997
		JP 10510530 T	13-10-1998
		US 5866589 A	02-02-1999
WO 9710212 A	20-03-1997	AU 7129596 A	01-04-1997
		EP 0853615 A	22-07-1998
		JP 10511113 T	27-10-1998